VOLUME 29 NUMBER 6

ARCHIVES

OF

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JUNE 15, 1922

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized on June 14, 1918.

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Archives of Internal Medicine

VOL. 29 JUNE, 1922 No. 6

PIGMENT METABOLISM AND REGENERATION OF HEMOGLOBIN IN THE BODY*

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The words "pigment metabolism" should mean the general exchange and balance in the body of all pigment substances—the income of pigment forming material, the story of pigment building in the body, the disposition of recognized end products in the body and the elimination of certain pigment complexes.

Any junior medical student can relate the true story of pigment metabolism in the human body. The medical textbooks have long retold the story as illustrated in Figure 1; and it seemed to be one of the facts in physiology which stood firm in the midst of progress and newer investigations. Its very age gave it respectability and true academic security of tenure. The time honored story is as follows: Certain food elements and iron are constructed in the bone marrow into a complex substance, hemoglobin. When the red cells are worn out or destroyed, the hemoglobin appears as bile pigment in a quantitative ratio. This bile pigment secreted into the intestine is changed to stercobilin and in large part excreted in the feces. Some of it may be absorbed and re-excreted by the liver; but, given a liver abnormality, it may escape the portal blood stream and be excreted by the kidneys as urobilin.

A number of recent investigations have modified this picture somewhat, as illustrated by Figure 2. Wilbur and Addis [1] suggest that with the absorption of stercobilin the "pyrrol complex" may be split off and reconstructed into hemoglobin. This is a very interesting hypothesis and would be an example of a very pretty conservation on the part of the body, but we shall review experimental observations which we believe rule out this suggestion.

Our conception of body pigment metabolism may, perhaps, be expressed diagrammatically as shown in Figure 3. One point in particular deserves notice in that we no not accept as proved that

* From the George Williams Hooper Foundation for Medical Research, University of California, San Francisco; Harvey Society Lecture, Jan. 7, 1922.

1. Wilbur and Addis: Arch. Int. Med. **13**:235 (Feb.) 1914.

there is any absorption of stercobilin from the intestine. Granting that urobilin may be formed in the liver, there is not a shred of evidence, clinical or experimental, that stercobilin is ever absorbed from the intestine. Most observers admit that a times urobilin may be formed in the liver (Wilbur, Addis and many others), but forget this fact when absorbed in a discussion of the formation of stercobilin in the lumen of the intestine. We believe that stercobilin in the intestine is as little concerned with this question of pigment metabolism as is the stercobilin in the feces or the urobilin in the bladder urine. Therefore in Figure 3 we know of no evidence for a line between the circles indicating urobilin and stercobilin.

We have published (Whipple & Hooper [2]) evidence that bile pigment is not necessarily related directly to destruction of red cells and hemoglobin. This is indicated in Figure 3 by a direct line from "pigment complex" to "bile pigment" and illustrates the relation of

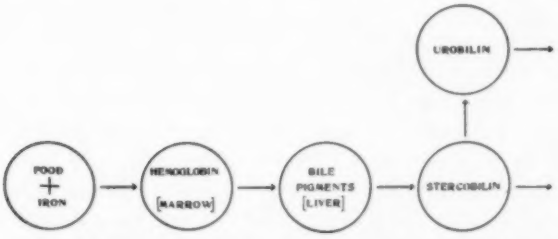

Fig. 1.—Pigment metabolism in the human body as formerly believed to occur.

bile pigment production to food and other factors which can modify pigment production quite apart from hemoglobin destruction. Granting that bile pigment production may be influenced by other factors than hemoglobin destruction, we see how absurd it is to draw conclusions unreservedly as to blood destruction from the analysis of stercobilin—for example, in pernicious anemia. The life cycle of the red cell has been established (Eppinger and Charnas [3]) on such flimsy evidence as the analysis of stercobilin.

That body protein as well as food factors are concerned in the production of bile pigment and hemoglobin is easily established by fasting experiments. Bile pigment excretion will continue during fasting periods, and, more than this, we have shown that hemoglobin will be formed in fasting periods not only sufficient for red cell maintenance but for actual increase above a moderate anemia level.[4] It is obvious

2. Whipple and Hooper: Am. J. Physiol. **40**:349, 1916.
3. Eppinger and Charnas: Int. of klin. Med., 1913, p. 78.
4. Whipple and Hooper: Am. J. Physiol. **45**:576, 1918.

that disintegration products of body cells are used in the upbuilding of hemoglobin and are related to the output of bile pigment, urobilin, stercobilin, and urochrome.

BILE PIGMENT

Much of the older work on the biliary pigments has been reviewed recently by Hooper and Whipple [5] and need not be discussed at this time. It has been claimed by some that hemoglobin introduced into the blood stream will be quantitatively excreted as bilirubin in the bile. Whipple and Hooper [6] have been able to show that no such quantitative relationship holds for hemoglobin and bile pigment. It seems very probable that much of the hemoglobin set free in the blood stream may be used in the body economy for a variety of purposes—among others the construction of hemoglobin for new red cells. For example,

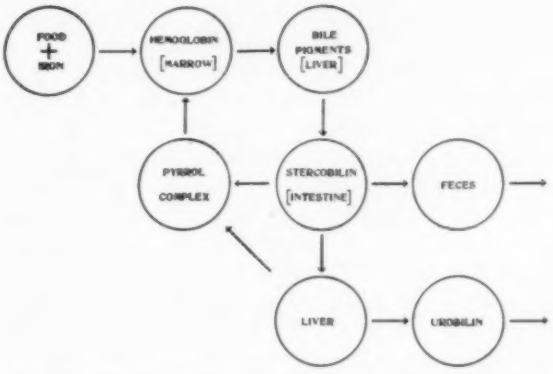

Fig. 2.—Pigment metabolism as modified by recent investigation.

it is sufficiently well established that intravenous injections of hemoglobin or the destruction of red cells in the body will aid in the recovery from simple anemia with consequent upbuilding of new hemoglobin.[7] It is very probable, however, that the hemoglobin in the blood stream is not used direct but only after being broken down to the unit structural factors—whatever these may be. This point is graphically illustrated by the double arrows between the "pigment complex" and "hemoglobin" in Figure 3.

It is now generally accepted that true bile pigment can be formed from hemoglobin within the body or by other than liver

5. Hooper and Whipple: Am. J. Physiol. **40**:332, 1916.
6. Whipple and Hooper: Am. J. Physiol. **43**:258, 1917.
7. Hooper, Robscheit and Whipple: Am. J. Physiol. **53**:263, 1920. Itami: Arch. f. exper. Path. u. Pharmakol. **62**:104, 1910. Itami and Pratt: Biochem. Ztg. **18**:302, 1909.

cells. Whipple and Hooper[8] showed that this transformation could be effected within two hours in the blood stream of the head and thorax with complete liver exclusion. The same workers[9] showed that hemoglobin can be transformed into bilirubin in the serous cavities within a period of twelve hours. McNee[10] has confirmed a part of this work. It is probable that the vessel endothelium and Kupffer cells are concerned in the vascular reaction. We believe that this reaction is not a physiologic curiosity but one of considerable importance in all conditions associated with escape of hemoglobin into the blood stream—for example, paroxysmal hemoglobinuria, malaria, toxic anemias, etc. Under such conditions we believe there is good evidence that much of the hemoglobin is changed to bile pigment and other substances quite apart from essential liver cell activity.

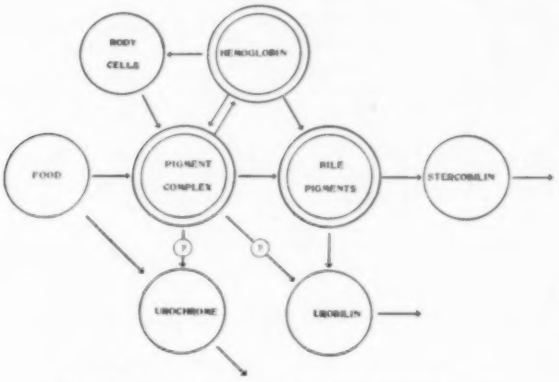

Fig. 3.—Conception of body pigment metabolism.

It is well established[2] that the bile pigment elimination in dogs can be increased by a change in diet—for example, a sudden change from a meat to a carbohydrate diet may increase the bile pigment elimination more than 50 per cent. This can be repeated time after time and it seems at least improbable that this reaction is dependent on blood destruction. We may explain this reaction, in part, as follows. The meat diet is normal for the dog. The increase in bile pigment excretion due to carbohydrate excess may represent an abnormal or alternative reaction—a deviation of pigment elements and construction into bile pigment for elimination. It is possible that some of these pigment elements concerned in this reaction might be

8. Whipple and Hooper: J. Exper. M. **17**:612, 1913.
9. Hooper and Whipple: J. Exper. M. **23**:137, 1916.
10. McNee: J. Path. & Bacteriol. **18**:325, 1913.

available under favorable conditions (anemia) for hemoglobin construction or under usual conditions (meat diet) for elimination elsewhere than in the bile. Urochrome is a possible end product of pigment elements and deserves much more study in normal and abnormal conditions.

The term "pigment complex" is used in this paper to indicate a group of substances which are essential parts of the mature body pigments. It is obvious that certain food factors contribute to this "pigment complex" as foods are directly concerned in the production of new hemoglobin and the formation of bile pigments and urochrome. It is equally clear that the body protein and cells contribute to this "pigment complex," as all body pigments are produced in measurable amounts in fasting periods. We believe that the evidence is sufficient to show that as hemoglobin disintegrates in the body it also contributes to the "pigment complex" and so influences, in a measure, the new formation of hemoglobin. It is probable that only a small amount of the destroyed hemoglobin is conserved in this fashion. The pyrrol nucleus seems to be one of the factors which must be concerned in this "pigment complex," and it is probable that all facts related to pyrrol metabolism will have a direct relation to the complicated body pigment metabolism. These points are illustrated graphically in Figure 3.

Bile pigments in the bile fistula animal are not increased by the feeding of fresh bile pigments or of fresh or cooked blood or of digestion products obtained from blood.[11] This might be assumed to be from lack of absorption. There is no evidence that bile pigment or stercobilin are absorbed from the intestine. However, it has been shown that the feeding of hemoglobin will influence the curve of new hemoglobin construction after anemias.[7] This indicates an absorption of substances which are concerned with the "pigment complex" but it is clear that these same factors do not influence the output of bile pigments in bile fistula dogs—at least under the conditions of our experiments. These experiments are much against the suggestion of Addis (Fig. 2) that there may be a conservation of bile pigment factors which are absorbed from the intestine and reconstructed into hemoglobin. Perhaps the strongest argument against the absorption of stercobilin and its utilization in body pigment construction (Fig. 2) is the fact that bile fistula dogs under observation continuously for two years or longer show no evidence of pigment lack, no anemia, no fall in pigment production and no reaction whatever to the feeding of bile pigments.

A study of the bile pigment output of the Eck fistula liver furnishes some interesting facts to consider at this time. Dogs with

11. Whipple and Hooper: Am. J. Physiol. **42**:256, 1917.

combined Eck and bile fistulas eliminate less bile pigment than controls—sometimes only from 30 to 50 per cent. of normal.[12] The Eck fistula liver is functionally inefficient and there is no direct contact with the portal blood. Both these facts may well contribute to this low pigment output, but the main point to emphasize is that the pigment output is influenced by liver function rather than by the amount of hemoglobin waste products formed in the body. We have ample evidence that various liver injuries will likewise depress bile pigment excretion—again, clear evidence that the liver has a constructive function in producing bile pigments rather than a simple passive eliminative function.

Bile fistula dogs with anemia give very interesting and complex reactions to hemoglobin injections.[6] In general, we may say that the elimination of bile pigments is not in any way parallel to the amount of hemoglobin injected. The same is true for control dogs with bile fistulas but no anemia. There is some evidence in these anemia experiments for conservation of certain of these pigment factors within the body. We may suspect a reconstruction of some of these factors into hemoglobin because of the anemia needs. There are some experimental data in favor of this explanation.

Certain of our bile fistula dogs have developed peculiar diseased conditions which may or may not be concerned directly with pigment metabolism. For example, certain dogs lose great amounts of inorganic salts from the bones, so much so that the ribs show very many "green stick fractures." These bones are reduced to mere elastic shells and the heavy long bones are likewise depleted of lime salts. There are many suggestive points in these experiments which are of peculiar interest at this time (diet and bony changes) but a discussion of this complex question must be postponed for the present.

Splenectomy in bile fistula dogs[13] gives reactions at times which are of the greatest interest to the hematologist. These dogs may show blood crises much like those observed in pernicious anemia. The color index may be very high for considerable periods—a most unusual condition in dogs. At times such dogs show maximum pigment production, which cannot be explained by destruction of red cells and hemoglobin. A specific experiment [Dogs 16-41, Table 69[13]] shows periods of great bile pigment increase—even six times normal per kilo body weight. To account for all this bile pigment as derived from hemoglobin we must postulate a complete destruction of all circulating hemoglobin every four or five days or less, or a daily red cell replacement of from 20 to 25 per cent. This is unthinkable in the light of

12. Whipple and Hooper: Am. J. Physiol. **42**:544, 1917.
13. Hooper and Whipple: Am. J. Physiol. **43**:275, 1917.

our knowledge of red blood cell regeneration in the dog, and we cannot imagine that all this pigment had been built up to hemoglobin before being broken down into bilirubin. Rather we wish to assume that the body is stimulated to a maximum production of pigment substances—in part, toward hemoglobin, in part, to bilirubin and, perhaps, to other pigment substances. The high color index indicates a maximum saturation of corpuscles with the pigment hemoglobin (refer to pernicious anemia below).

Study of the bile pigments present in human serum in health and disease has been reported by a number of investigators (Van den Bergh,[14] Brulé,[15] Blankenhorn[16] and many others). It is evident that there are various free and partially bound pigments in the blood plasma or serum. Some of these pigments may dialyze through a parchment membrane and others will not do so. The significance of these various types of pigments has been discussed at considerable length by the different workers, but as yet there does not seem to be complete accord as to interpretations. Much important information will undoubtedly come from this work but wherever possible a more extended study of the body, feces and urine pigments should be made simultaneously.

UROBILIN

In discussing the pigment substances in the urine we wish to use the term urobilin to include the closely related substance urobilinogen. We use the term stercobilin to indicate the same substances in the feces. It seems to be accepted generally that stercobilin is formed in the intestine due to bacterial action on bile pigments. It is assumed solely on indirect and incomplete evidence that stercobilin is, in part, absorbed from the intestine. We believe there is no evidence for this assumption and much against it. This absorption of stercobilin should be discredited until such time as some positive evidence of intestinal absorption is brought forward. It is admitted by most clinical observers that urobilin is present at times in human bile in the liver[1] or gallbladder.[17] We have observed the presence of urobilin frequently in bile fistula dogs during fasting periods—in fact, this may seriously interfere with experimental work on bilirubin.[18] We believe that all evidence favors the production of urobilin in the liver and bile passages (cholangitis), its absorption at times into the blood stream from the liver and subsequent appearance in the urine. It is probable that

14. Van den Bergh: Der Gallenfarbstoff im Blute, 1918.
15. Brulé: Recherchés récentes sur les icterus, Paris, Masson et Cie, 1919.
16. Blankenhorn: Arch. Int. Med. **27**:131 (Jan.) 1921.
17. Straus and Hahn: München. med. Wchnschr. **67**:1286, 1920.
18. Whipple, Hooper and Robscheit: Am. J. Physiol. **53**:151, 167, 1920.

urobilin, like bilirubin, at times is produced in tissues other than the liver (blood extravasations, pneumonia, etc.).

We do not wish to deny the value of urobilin determination on the urine, feces and bile, but the deductions drawn from such observations should be made with a proper conception of the various reactions concerned; and absorption of stercobilin is not one of the factors to be accepted at present. Studies of urobilin in the urine may indicate certain liver abnormalities or pigment disturbances in other parts of the body. Analyses of stercobilin give figures of great interest but high figures may indicate overactivity of the liver in pigment production rather than excessive blood destruction with elimination through the liver of bile pigments or urobilin. The analysis of fresh human bile obtained by means of the duodenal tube will give facts of much value (Lyon and others [19]). It should be remembered that such samples are suitable only for qualitative analysis. The amount of dilution can never be determined but the ratio of bile pigments to bile acids may be of considerable significance, although difficulties in analysis are present. The presence of urobilin and abnormal elements in the duodenal bile may contribute facts of great value for a complete understanding of a complicated disease picture.

The various methods for determination of urobilin or stercobilin are admittedly unsatisfactory. Moreover, certain changes in the feces may make analysis inaccurate or quite impossible (constipation, diarrhea, etc.[1]). Attempts aimed toward accurate quantitative extraction are reported by Hausmann,[20] Goiffon,[21] Baumann [22] and others. When a simple and accurate quantitative method is at hand the work on these problems will be greatly facilitated. A method to give complete satisfaction in stercobilin estimations must give accurate figures not only for stercobilin but its various related substances which confuse the picture in simple complications like constipation and diarrhea.

UROCHROME

Urochrome is the stepchild of the pigment family. Numerous theories as to its origin have been advanced but it can safely be asserted that its parentage is doubtful. It has been suspected that urochrome was related to urobilin, to blood pigments, to urea and to food pigments. These views have recently been reviewed by Pelkan,[23] whose work indicates an important relationship of urochrome to food

19. Lyon: J. A. M. A. **73**:980 (Sept. 27) 1919.
20. Hausmann: Ztschr. f. exper. Path. u. Therap. **13**:373, 1913.
21. Goiffon: J. Pharmacol. Chem. **21**:286, 1920.
22. Baumann: Arch. Int. Med. **28**:475 (Oct.) 1921.
23. Pelkan: J. Biol. Chem. **43**:237, 1920.

protein. He brings evidence that carotin is not concerned in the urochrome excretion.

Urochrome contains the pyrrol group,[24] which is always of interest in any pigment work. There has been no extensive work done to study the appearance and relationship of this pigment with other important body pigments in health and disease. It is at least possible that urochrome forms one of the avenues of disposal of pigment elements ("pigment complex") even before such substances are built into hemoglobin or bile pigments. These possibilities do not preclude fluctuations of urochrome due to large intake of foods rich in pigment forming materials. This substance should be studied simultaneously with other pigments (blood and bile) in health and disease, in clinical and experimental conditions.

LIPOCHROME

Lipochrome is a peculiar pigment which is thought to have merely a passive function in the body with no relationship to the urobilin, urochrome or other pigments containing the pyrrol nucleus. Schulze [25] states that lipochromes are very closely related to the yellow radicle of chlorophyll and members of the group of carotinoid pigments including carotin and xanthophyll. The lipochromes are soluble in fat and fat solvents. Dolley and Guthrie [26] state that these lipochromes can be removed from the body fat almost completely by diet periods free from carotin intake. Van den Bergh [14] states that the lipochrome content of the blood varies with the diet intake of these food pigments. It is well known that the serum of diabetics is rich in lipochrome pigment, and he attributes this to diet factors. At present we have no reason to suppose that the lipochromes have any direct relationship to the other body pigments, but we should not close our minds to this possibility, especially in disease conditions, for example, hemochromatosis and pernicious anemia.

HEMOGLOBIN

Hemoglobin is without question the most important and interesting of all the body pigments. Much of the interest in other body pigments comes from a relationship known or assumed to exist between these various pigments and hemoglobin. A very closely related or identical substance, myohematin (muscle hemoglobin) exists in the striated muscle tissue of the body and undoubtedly plays an important part in the rapid exchange of oxygen and carbon dioxid between the functioning muscle protoplasm and the circulating hemoglobin. Myohematin will not be considered in detail in this paper, but we should always keep this

24. Weiss: Med. Klin. **13**:659, 1917.
25. Schulze: Sitz. Ges. Nat. Freunde, Berlin, 1914, p. 398.
26. Dolley and Guthrie: Science **50**:191, 1919.

substance in mind when we study various gases (for example, carbon monoxid) which are absorbed by hemoglobin in the body. The genesis of myohematin is of fundamental importance, and we have no right to assume that the bone marrow cells are concerned in its production. Is this substance formed from its very elements by the activity of the muscle tissue alone? Or is some partially built up "pigment complex" utilized by the muscle tissue in building this most complex substance? How rapidly is the myohematin used up in the body as compared with the daily wastage and repair of circulating hemoglobin? It will be of great importance to study various conditions in which myohematin may be present in abnormal amounts. It has been pointed out recently [27] that this substance usually amounts to about 10 per cent. of the total body hemoglobin, but much more work is needed to ascertain the conditions under which the myohematin content may be found to depart from normal. Such studies will give information of much value for the complete understanding of the body pigment metabolism. Hoagland [28] has recently completed experiments to show that aseptic anaerobic autolysis of beef muscle will produce measurable amounts of hematoporphyrin. He suggests that this is a normal reduction product of hemoglobin in the body and a substance intermediary to the final end product, bilirubin.

In the adult human it is generally assumed that hemoglobin is fabricated in the protoplasm of red cell groups within the bone marrow. We have suggested that other tissues (for example, the liver) may be concerned in building up "parent pigment substances" which are essential to the proper construction of mature red cells containing hemoglobin. It is worth while reviewing a few facts concerning the development of red cells in the embryo. Sabin [29] has pointed out that blood cells in the second day chick embryo develop from the endothelial cells and angioblasts. Hemoglobin is present at this time but the liver is not functionally active. This seems at first sight to indicate that endothelial cells can produce red cells and the pigment hemoglobin. This may in fact be true but we must not forget the yolk sac with its various storage factors developed by the mature hen and drawn on continuously by the developing embryo. The endothelial cell, however, may be active in a variety of the body pigment reactions and can almost certainly produce bilirubin from hemoglobin.[8]

Therefore, it is possible that these cells have a capacity to build up pigment substances and so take part in hemoglobin production. We recall, too, the interesting relationship in early fetal life (human)

27. Smith, Arnold and Whipple: Am. J. Physiol. **56**:336, 1921.
28. Hoagland: J. Agricul. Res. **7**:41, 1916.
29. Sabin: Anat. Rec. **13**:199, 1917.

between the liver cells and the islands of blood forming cells. This would indicate a possible relationship between the liver cell, the Kupffer cell and the developing red blood cell. It is, of course, possible that this relationship continues through the agency of the circulation during adult life.

DIET FACTORS AND HEMOGLOBIN

We have long been interested in the influence of various diet factors on the regeneration of red cells and hemoglobin during periods of simple anemia in dogs experimentally produced by hemorrhage. This work was begun by C. W. Hooper and me as an outgrowth of our bile pigment investigations and later continued with the cooperation of F. S. Robbins. The investigation is now being continued by Robbins and Whipple. We may refer to certain publications [18] for much of the experimental detail, methods, protocols, etc. At the outset it seemed obvious from simple experiments that hemoglobin regeneration could be influenced easily by a variety of diet factors. We thought it highly desirable to work with animals of sufficient size and suitable type so that blood could be obtained readily for various analyses by venous puncture. Dogs were obviously best suited for these experiments. The removal of small blood samples is very easy and does not complicate the regeneration curve as the amounts removed are so small as compared with the blood volume (from 800 to 1500 c.c.). These dogs are omnivorous and will eat readily all types of food mixtures. Our routine experiments included careful determinations of blood volume, hemoglobin and red cell hematocrit, red cell counts from blood drawn by venous puncture and body weight.

Our experimental data give numerous examples to show the necessity of such complete determinations and the mistaken deductions which may be derived from incomplete experiments. This applies particularly to experiments of long duration where the differences between any given group and the controls are but slight. The general procedure is as follows: A group (usually four) of normal dogs is standardized (blood volume, red cell hematocrit, red cell count, etc.). These dogs are then bled one-fourth of their total blood volume on two successive days, at times a third bleeding is used. After a rest of one day they are again standardized and placed on the experimental food mixture. Complete determinations are done thereafter each week until the end of the experiment.

Two characteristic tables (Tables 1 and 2) may be cited as examples of the wide differences in hemoglobin regeneration which may be associated with sugar feeding (Table 1) and with meat feeding (Table 2). We see that the blood regeneration is but slight—a slight increase over and above the maintenance factor in red cells and an

TABLE 1.—Blood Regeneration After Sugar Feeding

Dog 17-28. White bull, female, adult.

Date, 1917	Pigment Volume = Hb. per Cent. Times Blood Volume	Blood Volume	Plasma Volume	R. B. C. Volume	R. B. C. Hematocrit	Hb.	Color Index	Hb. Index	R. B. C., Million	W. B. C.	Weight	Blood per Kilogram	Remarks
		C.c.	C.c.	C.c.	%	%					Kg.	C.c.	
1/19	1,620	1,500	600	900	60.0	108	0.76	1.80	7,1	7,4	11.00	129	Fasting
1/20	Bled 375 c.c.												
1/22	Bled 270 c.c.												
1/23	Bled 105 c.c.												
1/24	588	900	603	306	34.0	61	0.80	1.79	3,8	7,8	10.40	87	
1/24	Diet: 50 gm. cane sugar, 25 gm. glucose, 400 c.c. water												
2/ 2	717	1,121	684	437	39.0	64	0.62	1.64	5,2	7,2	9.40	120	*Anis.
2/ 9	626	1,027	637	390	38.0	62	0.65	1.63	4,8	6,2	8.90	115	
2/16	634	961	586	375	39.0	66	0.59	1.69	5,6	10,0	8.50	113	Diarrh.+
2/23	541	933	562	373	40.0	58	0.56	1.45	5,2	9,0	8.00	117	

* Anisocytosis of red cells.
Blood volume with dry oxalate. Hemoglobin with Sahli tubes.
Hemoglobin index equals hemoglobin per cent. divided by red cell hematocrit per cent.

TABLE 2.—Blood Regeneration After Beef Heart and Liver

Dog 18-116. Bull mongrel, female, young adult.

Date, 1918-1919	Pigment Volume = Hb. per Cent. Times Blood Volume	Blood Volume	Plasma Volume	R. B. C. Volume	R. B. C. Hematocrit	Hb.	Color Index	Hb. Index	R. B. C., Million	W. B. C.	Weight	Blood per Kilogram	Remarks
		C.c.	C.c.	C.c.	%	%					Kg.	C.c.	
12/ 2	2,130	1,720	805	907	52.7	123	0.56	2.32	11,4	1,14	14.90	115	
12/ 2	Diet: Crackermeal and milk												
12/ 2	Bled 430 c.c.												
12/ 4	Bled 430 c.c.												
12/ 6	989	1,182	803	369	31.2	79	0.57	2.54	6.9	21,2	14 55	81	
12/ 7	Bled 300 c.c.												
12/ 9	776	1,360	930	323	25.6	62	0.84	2.38	3,7	17,5	13.95	90	
12/ 9	Diet: 256 gm. cooked beef heart;* 610 gm. cooked beef liver*—100 calories per kilo												
12/16	1,082	1,330	844	476	35.8	81	0.88	2.25	4.6	18,2	14.55	91	
12/22	1,890	1,685	860	818	48.5	112	0.57	2.30	9,9	11,5	15.25	110	
12/30	2,270	1,648	747	902	54.7	138	....	2.50	....	....	15.50	106	

* Meat cooked, fat and connective tissue removed and ground.
Hemoglobin index equals hemoglobin per cent. divided by red cell hematocrit per cent.

even smaller increase in hemoglobin within a period of four weeks. The contrast with meat and liver feeding is striking (Table 2) which shows complete return to normal in a period of three weeks. Between these extremes are all types of reaction, and it is easy to understand that a diet containing several food factors may give a complicated reaction. It is easy to understand that one food factor may be inert in this reaction and a second factor may likewise be inert but the two together may have a distinct influence on the curve of red cell and hemoglobin regeneration. For this reason it is necessary to test a given factor under a variety of conditions (supplementary feeding, etc.) before we can feel sure that we understand its reaction under anemia conditions. This is one of several reasons why the accumulation of convincing experimental data is so time consuming. We cannot accept the experiments of Downs and Eddy,[30] who report a positive influence of secretin on the production of red cells in anemia. They record only the red cell count with no figures for red cell hematocrit, hemoglobin or blood volume observations. That secretin may influence the red cell and hemoglobin production may be true but this is neither proved nor disproved by their experiments.

MEAT

Our experiments show that diets of cooked beef muscle or cooked beef heart are very favorable for a rapid regeneration of red cells and hemoglobin (Table 2 and others[31]). Cooked liver ranks with cooked muscle, and these food factors will effect a prompt reconstruction of the anemia picture to normal. These favorable diet factors are also potent when given after long periods of anemia and unfavorable diet intake. This is the severest test for any diet factor as to its influence on red cell and hemoglobin reconstruction. Certain diet factors may give a favorable reaction if given at once after the anemia is produced but may give an unfavorable reaction if given at the end of a long period of anemia and unfavorable diet intake.[31] Meat extracts (commercial) are inert and possess none of the factors which influence red cell and hemoglobin regeneration.

FOOD GRAINS

The common food grains (wheat, barley, rice) in the form of cooked bread or crackers do not furnish many factors which promote red cell regeneration. Full diets of these materials with skim milk may effect a slow rise in the level of hemoglobin and red cells which finally may reach normal in from six to eight weeks. More com-

30. Downs and Eddy: Am. J. Physiol. **58**:298, 1921.
31. Whipple, Robscheit and Hooper: Am. J. Physiol. **53**:236, 1920.

monly the return toward normal will not exceed 90 per cent. of the initial level before the anemia is produced by bleeding. Casein and skim milk may be ranked with these food grains as regards their influence on hemoglobin regeneration and we may say that, as a rule, these foods do not return anemia animals to a high red cell and hemoglobin level.

FASTING

A comparison of anemia fasting experiments with sugar feeding experiments shows that anemic dogs actually produce more red cells and hemoglobin during fasting periods than during periods of sugar feeding. The question of the "sparing action" of carbohydrates comes into this reaction, but we must refer the reader to reviews [18] of this subject in recent papers.[32] There is evidence from these experiments that the body conserves with much care the various pigment construction units, which are then recast into red cells and hemoglobin. It is well to keep in mind the fact that normal dogs during periods of zero nitrogen intake (fasting or sugar feeding) are able to form hemoglobin and red cells over and above the considerable amount needed for daily wastage and repair—also are excreting considerable amounts of bilirubin, stercobilin and urochrome. These must all come directly or indirectly from the host's protein. This careful conservation of red cell and hemoglobin construction factors must be of considerable importance in the body economy.

IRON

Iron furnishes a never failing topic for discussion by internist and physiologist alike. Clinical opinion favors the use of iron in simple anemias, but we question whether this treatment is based on sound evidence. At least, the treatment does the patient no harm and may soothe the doctor's conscience, but we can find no convincing evidence that it gives patients with secondary anemia any real benefit. This discussion does not concern chlorosis, which appears to be a distinct disease entity. All the experimental evidence indicates that iron is inert in secondary anemias and has no influence on blood regeneration. Our experiments [33] indicate that iron in the form of Blaud's pills is inert.[7] Ferric citrate and ovoferrin have little or no influence on blood regeneration—nothing to compare with favorable food factors (meat). Hemoglobin, given by mouth, intraperitoneally or intravenously, does influence the curve of red cell and hemoglobin regeneration in a positive fashion but not to the extent noted with potent diet factors (meat). The iron may be concerned in this reaction but there is even more

32. Davis and Whipple: Arch. Int. Med. **23**:689 (May) 1919.
33. Whipple and Robscheit: Arch. Int. Med. **27**:591 (May) 1921.

evidence in favor of the pyrrol complex. Likewise, arsenic in sodium cacodylate or Fowler's solution is inert in these anemia periods. We believe it will repay the clinical workers to record careful observations on anemic patients, paying particular attention to various diet factors proven to be potent in controlled experiments.

The relation of hemoglobin and chlorophyll has given rise to much speculation in the past and there are many interesting possibilities which call for more work. It has been pointed out that under usual conditions iron is necessary in plant metabolism for chlorophyll production but does not form a part of the chlorophyll nucleus.[34] In the absence of iron plants can form chlorophyll if there is a supply of pyrrol material.[35] These observations are of particular interest when we consider the influence of certain plant leaves rich in chlorophyll on the blood regeneration of anemia dogs (see below). But the evidence that iron is directly concerned in this reaction is not convincing.

It has been reported by Cloetta [36] that the iron present in hemoglobin is not absorbed from the dog's intestinal tract, and he is able to recover the iron quantitatively after blood feeding. Weber [37] has reported experiments to indicate that iron lactate is inert in anemia periods in experimental animals. However, he did not control his diet and reports on hemoglobin values only. The anemia was produced by pyrodin. His experiments are not convincing but give no evidence that this iron salt is potent. Musser [38] has furnished more evidence that iron is inert under experimental conditions. Iron was given as ferrous sulphate in capsules and the dogs rendered anemic by repeated bleedings. He gives complete data on hemoglobin, red cell count, resistance of red cells to hypotonic solutions and blood volume. It is, perhaps, unfortunate that a mixed diet of hospital food scraps was used in all these experiments. As diet factors are important it is very desirable that the investigator knows the amount and type of food intake. A mixed diet gives an opportunity for much variety and also choice by the animal. As a rule, the blood regeneration is very rapid on a mixed diet and gives less opportunity to demonstrate the influence of any given factor on blood regeneration. Some experiments should be included to show the influence of the given drug when administered during a long period of feeding on a diet unfavorable to rapid blood regeneration—for example, a 75 calory per kilo diet of bread and skim milk.

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34. Moore: Proc. Roy. Soc. Lond. **87**:556, 1914.
35. Oddo and Pollacci: Gazz. Chim. Ital. **50**:54, 1920.
36. Cloetta: Arch. f. exper. Path. **37**:69, 1895.
37. Weber: Ztschr. f. Biol. **70**:168, 1920.
38. Musser: Arch. Int. Med. **28**:638, 1921.

FATS

Unpublished experiments of Robbins and Whipple indicate that lard is inert in various diets, and influences in no degree the regeneration of red cells and hemoglobin in anemic dogs. Numerous experiments with cod liver oil give no evidence that this oil influences blood regeneration. In striking contrast stand the experiments with butter fat, which indicate that under certain conditions some substance in butter fat is able to influence in a striking way the curve of hemoglobin regeneration and hasten the production of hemoglobin and red cells. When we admit that butter feeding is potent in anemia regeneration of hemoglobin, we can scarcely admit that it actually is built into the hemoglobin molecule. But it may act in some way to facilitate the linkage of the various complexes which go into the large hemoglobin molecule. We have not as yet sufficient data on the influence of butter feeding upon the output of other body pigments during anemia periods.

FISH

Through the friendly cooperation of the California Packing Corporation and the Alaska Packing Corporation we were able to test a variety of food fish. These experiments will be published in the near future. The highly pigmented cooked salmon muscle was used and in a variety of diet tests was shown to be inert in anemia experiments. It is of particular importance to note that this muscle pigment of the salmon is not concerned in the upbuilding of hemoglobin in dogs. We have some evidence that the myohematin of beef muscle is actually concerned in hemoglobin regeneration, which is so rapid after beef feeding. Whale meat was tested and found to act exactly like beef muscle or other striated mammalian muscle. Clams, like fish, are inert in anemia experiments.

VEGETABLES

The data concerning vegetables will be published shortly by Robbins and Whipple. A number of vegetables have no effect on the curve of red cell and hemoglobin regeneration after anemia. Carrots are inert and deserve particular attention because of their high content of carotin, a food pigment which does enter into the body fluids and tissues. Dehydrated celery, parsley and Brussels sprouts are likewise inert, and it is improbable that the dehydration was responsible for the negative reaction as dehydrated spinach is positive and exerts its usual influence on the hemoglobin reaction. Fresh beet tops are negative, as compared with fresh spinach, which is positive and even more potent than the dried spinach meal. Canned spinach is somewhat less potent than is the freshly cooked material. These observations show that by this physiologic test there is a distinct difference

between the chlorophyll of sprouts, celery, parsley, and beet leaves as contrasted with the chlorophyll of spinach.

PERNICIOUS ANEMIA

This is a diseased condition, little enough understood, which is of the greatest interest to any person investigating general body pigment metabolism. Let us examine the facts as known, paying particular attention to this question of pigment metabolism. We find an excess of pigment substances everywhere in the body—increase of pigments in the liver cells, blood stream, bone marrow, feces and, at times, in the urine. There is a high hemoglobin index or we may say the red cells are saturated with hemoglobin as contrasted with the 50 per cent. hemoglobin content of a simple anemia. This suggests that the body has an excess of pigment material available and is producing various pigment substances at an abnormal rate of speed—compare the experiment (the splenectomy bile fistula dog, No. 16-41 [13]) which showed a high color index and enormous overproduction of bile pigment.

We are told that the stercobilin analysis in a case of pernicious anemia is an index of blood destruction. Let us examine some of these figures and, further, let us assume the normal red cell count as 5,000,000 and the pernicious anemia count as 1,000,000 for the sake of simplicity of comparison. If the anemia red cells disintegrate at the same rate of speed as the normal control, and if these products result in bilirubin and then stercobilin we must say the stercobilin figures should be one-fifth of normal. But the stercobilin figures during periods of remission in pernicious anemia often exceed twice or three times normal stercobilin excretion, making no allowance for similar pigments in the urine. This can only mean that the pernicious anemia patient with one-fifth the number of red cells and two or three times the amount of stercobilin output must regenerate its total red cell mass every three days instead of the assumed normal of every thirty days. The normal replacement factor for red cells and hemoglobin is believed to be 3 per cent. per day.[39] We must postulate from 30 to 40 per cent. replacement of red cells per day in a pernicious anemia case if we persist in explaining the stercobilin content as being due to blood destruction. Those who wish to accept this explanation are welcome to do so, but it would be a fleeting and troublous life period endured by the red cell in pernicious anemia!

Ashby [40] has published recent observations to show that the life cycle of the human red cell is variable and may be thirty days or at

39. Ashby: Jour Exper. M. **29**:267, 1919.
40. Ashby: J. Exper. M. **34**:127, 1921.

times 100 days. Further than this she submits observations which indicate that in pernicious anemia the red cells exist in the circulation at least as long as in the normal human case and perhaps for a longer time. She questions the importance of an increased blood destruction in producing the anemia of this disease.

We prefer to explain the observed facts as done in Figure 3, assuming that there is a great stimulus within the body for pigment production. It may well be that there is an overproduction of pigments, including hemoglobin and bile pigments and other abnormal pigments. For example, in certain cases of pernicious anemia Hooper and Whipple have observed an unusual pigment in gallbladder bile obtained at necropsy—a pigment which must be treated with active acetaldehyd before it will give the usual bile pigment tests. It is highly probable that this pigment, after a stay in the intestine, would be reduced to stercobilin and take part in the familiar high reading of stercobilin in such cases.

Our conception of pernicious anemia is that there is a scarcity of stroma building material or a disease of the stroma forming cells of the marrow which limits the output of red cell framework. There is plenty of pigment material (an excess in fact) as evidenced by the high color index or the saturation of the red cell with hemoglobin. Wherever we meet with a high color index we should suspect some deficiency in stroma construction or some overproduction of body pigments including hemoglobin. Conditions of malignancy, for example, with the hematology of pernicious anemia should yield information of value when examined with these points in mind. Nothing in this paper should be construed as minimizing the importance of stercobilin analyses for we are confident that such information is of great value. High stercobilin figures may be a very valuable diagnostic aid in obscure cases of pernicious anemia, as claimed by Hausmann and Howard.[41] That these figures indicate a corresponding destruction of red cells may be doubted and an overproduction of pigment may be a safer assumption.

Under usual secondary anemia conditions we know that this physiologic anemia stimulus causes a rapid production of both stroma and hemoglobin, the production of the stroma even outstripping that of the hemoglobin, as indicated by the low color index. It is possible that stroma production in the body may be fatigued more easily, as suggested by certain anemia conditions of long standing, which may show periods of high color index and a hematology suggesting pernicious anemia. Such cases are deserving of particular attention and a most careful study of the complete pigment metabolism.

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41. Hausmann and Howard: J. A. M. A. **73**:1262 (Oct. 25) 1919.

The experiments of McMaster and Haessler [42] may have an interesting bearing on some of these questions. They show that in rabbits the injection of hemoglobin intravenously is a stimulus to the extension of bone marrow tissue in the long bones of the experimental animals. Simple bleeding does not stimulate to the same degree this "spread" of the bone marrow. They believe that there is no evidence for direct utilization of the injected hemoglobin, which is probably broken down before use. So it is possible that the pigment construction factors or "pigment complex" may be radicles which determine the bone marrow spread.

HEMOCHROMATOSIS

This disease is characterized by abnormal deposits of various pigments in many body cells and tissues. By most writers it is thought that this increase in body pigments is to be explained by a great increase in blood destruction. The mere fact that there is no evidence to support his hypothetical increased blood destruction has not deterred writer after writer from this assumption. Sprunt [43] is probably the first writer to object to this interpretation, and he points out convincingly the entire lack of evidence for any increase in red cell destruction—further that the evidence favors some profound disturbance in body metabolism which permits the deposit or production of various pigments in the protoplasm of various body cells. MacCallum [44] has shown the presence of iron in the cystoplasm of ferment forming gland cells of all descriptions. It is interesting to recall the presence of abnormal iron containing pigments in these same cells in cases of hemochromatosis. The liver and pancreas are especially involved in this reaction, and the liver may contain 100 times the normal content of iron. Various observers record normal stercobilin elimination in cases of hemochromatosis. Wilbur and Addis [1] report a long series of observations on a case of hemochromatosis to show normal stercobilin figures and fluctuating amounts of urobilin in the urine. The necropsy disclosed cirrhosis of the liver and the familiar picture of this disease. It would be interesting to speculate about the pigment abnormalities in hemochromatosis, but we must recall that actual observed facts are but few in number. It can be said, however, that there is no evidence of an increase in red cell and hemoglobin destruction. Stercobilin elimination may be normal but we do not know anything as to iron intake and elimination. It will be of great interest to study the various pigment factors in the blood, urine and tissues. It is, at least, possible that the usual paths of pigment elimination and disposal are, in part, blocked at the source

42. McMaster and Haessler: J. Exper. M. **34**:579, 1921.
43. Sprunt: Arch. Int. Med. **8**:75 (July) 1911.
44. MacCallum: Ergebn. d. Physiol. **7**:552, 1898.

so that these pigments which may be present in various cells in traces are unable to escape and heap up within the cell protoplasm. This explanation suggests that various cell protoplasm may at times be concerned with the building up of certain pigment substances rather than with a simple passive storage. We may choose to look on this disease as resembling diabetes in certain respects—one disease with an inability to handle the carbohydrates, the other disease associated with abnormal metabolism of pigment factors. Certain end products are toxic in the first instance (diabetes) and again other products accumulate in the body cells (hemochromatosis) to their detriment and final destruction.

In this connection we wish to refer to experiments of Rous and Oliver,[45] who induced plethora in rabbits by intravenous injection of red cells. After months these animals developed siderosis of the liver, kidney and other tissues. Their experimental findings in animals have many points of similarity to those observed in human cases of hemochromatosis. Their conception that the essential disease factor in hemochromatosis lies in the liver does not wholly satisfy the writer, but their experiments bring some support to the explanation advanced above in favor of a disturbance of the whole intracellular pigment mechanism.

CONCLUSION

In conclusion, we may repeat that the various body pigments have interesting relationships which, perhaps, are not as simple as commonly believed. There may be at times a parallel increase or decrease of related pigments. We wish to make clear our conception of an underlying "pigment complex" which may be an intermediary stage in the development of mature pigments. Perhaps all pigment construction units pass through this stage and, depending upon supply and demand, are used to construct hemoglobin or bile pigment or are discharged as urobilin or urochrome or related pigments, as illustrated in Figure 3.

What may be the fundamental stimulus for pigment manufacture in the body is for future work to determine. The most important single point which we wish to emphasize is that pigment production depends upon constructive body cell activity—a dynamic function which concerns the formation of hemoglobin and bile pigments as well as urobilin and urochrome.

We recall that the output of bile pigment in the dog may be influenced by a variety of food factors but not by the feeding of bile pigment or hemoglobin. Bile pigment output depends on liver

45. Rous and Oliver: J. Exper. M. **28**:629, 1918.

functional activity, and we believe it is a product of liver activity not solely a passive elimination product coming from defunct hemoglobin. Splenectomy and bile fistula combined may give a maximum pigment output and a clinical picture resembling in some respects pernicious anemia. There is convincing evidence that stercobilin is not absorbed from the intestine and further that urobilin as observed in the urine is formed in the liver or body tissues, not absorbed from the intestine. Urochrome is a pigment too little studied. It may represent a shunt for pigment building material not utilized in the body. Lipochrome seems to be an inert pigment taken in with the food and slowly eliminated.

Hemoglobin regeneration following anemia may be influenced by a great variety of diet factors. Among the potent factors exerting a positive influence on hemoglobin stand, first, red meat and cooked liver, hemoglobin and butter fat. Then come spinach and full diets of common food grains and milk. Practically inert are other chlorophyll containing vegetable leaves—celery, parsley, beet tops and sprouts. In the same negative group are fish and clams, onions and beets and animal fats, including lard and cod liver oil. Iron and arsenic in the common drug preparations are likewise inert under these conditions.

Pernicious anemia and hemochromatosis show abnormalities of pigment formation and disposal. We believe these two diseases have this in common—a definite overproduction of pigment in the body but not an increased destruction of hemoglobin and red cells. These are pigment abnormalities which deserve the most careful study from this point of view. Such studies should be sufficiently comprehensive to include simultaneous observations of these pigment elements in the blood, feces and urine, also in the bile and body tissues whenever possible.

It may be that this paper is too speculative, but hypotheses are of some value for further work even if there be little or no truth in them. I hope to furnish more data in the near future bearing on these questions.

OCHRONOSIS

WITH A STUDY OF AN ADDITIONAL CASE *

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Ochronosis is the name given by Virchow in 1866 to a condition characterized by the pigmentation of the cartilages, ligaments, tendons and of the intima of the large blood vessels of the body. In this first reported case the pigment deposits appeared light gray, brown and, in places, black. On thin section, however, the pigment was everywhere found to be yellow or yellow-brown and for this reason the condition was called ochronosis.

Since then, forty additional cases have been studied. From the observations made it may be stated that ochronosis is a condition dependent on a disordered metabolism of phenol or some of its derivatives; characterized by a pigmentation of the cartilages, fibrocartilages, fibrous tissues and epidermis, as well as of areas of degeneration, notably atherosclerotic plaques, albuminous masses and concretions. A further characteristic is the presence of a dark urine due to alkapton, derivates of phenol or to melanin.

The cases of ochronosis may be divided into: (a) those due to the circulation in the blood of certain aromatic compounds with the excretion in the urine of homogentisic acid; (b) those due to the circulation in the blood of certain aromatic compounds with the excretion in the urine of melanin; (c) those due to the circulation in the blood of certain aromatic compounds following the external use of phenol.

The metabolic disorder responsible for the ochronosis in the first group is a congenital one and characterized by an alkaptonuria. More than one-half of all the ochronosis cases observed are in this group. The metabolic disorder responsible for the ochronosis in the second group results in an excretion in the urine of melanin. Only a few of the ochronosis cases are in this group. The metabolic disorder responsible for the ochronosis in the third group is an acquired one dependent on the prolonged external use of phenol. Eleven of the ochronosis cases observed are in this group.

Twenty-two of the cases in the literature are females; nineteen are males. The average age of the patients at the time of diagnosis was about 51 years. The youngest patient was 23 years of age. There

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* From the Montefiore Hospital for Chronic Diseases.

* Part of the expenses of this publication were defrayed from a fund left by the late Dr. H. S. Oppenheimer.

is a tendency for this condition to occur in families where there has been inbreeding.

The diagnosis offers no difficulty. The cartilages of the ears and nose have a bluish tint. The fibrous tissue, especially about small joints, has a bluish gray appearance. There may be dark pigment deposits in the sclerae and patches of pigmentation of the skin. There is an excretion of dark urine or urine which turns dark on standing, due to the presence of alkapton body or derivatives of phenol, rarely of melanin. The pigment may be excreted to some extent by sudoriferous and ceruminous glands.

The most frequent complications in ochronosis are: (a) deforming arthritis of the spine or larger joints, and (b) cardiovascular lesions.

HISTORICAL RÉSUMÉ

1. *Clinical.*—The early cases of ochronosis were recognized clinically by the pigmentation of the external cartilages. In 1892 V. Hanseman reported a case in which dark urine was passed. Examination of this urine was negative for alkapton body and melanin. In 1902 Albrecht and Zdareck, reporting the seventh case in the literature, called attention to the association of ochronosis with alkaptonuria. In 1904, Osler likewise reported two cases of ochronosis with associated alkaptonuria. No further observations on the nature of the process were recorded until Pick reported a case of ochronosis undoubtedly due to the prolonged external use of phenol. From his chemical study in cases associated with alkaptonuria and in one following chronic phenol poisoning, Pick concluded that in the ochronosis of endogenous origin (congenital, associated with alkaptonuria) a melanin is formed by the action of an enzyme on circulating homogentisic acid and tyrosin, and that in the exogenous form (due to phenol poisoning), a melanin is formed by the action of an enzyme on circulating hydroquinone and pyrokatechin. This explanation of ochronosis, advanced by Pick in 1906, has received no appreciable modification since. In 1908 Gross and Allard reported a case of ochronosis with alkaptonuria in which there was a deforming arthritis of the larger joints. Contrary to Virchow's belief that the pigment was deposited in the inflamed cartilage of the affected joints, they maintained that these arthritic changes were specifically due to the irritation of the deposited pigment. More recently, Söderbergh [1] called attention to a deforming arthritis of the spine in four cases of ochronosis with alkaptonuria. Attention has also been called [2] to the frequent association of cardiovascular lesions with ochronosis and it has been suggested that these changes, like the arthritic ones, are primarily dependent on the metabolic disorder.

1. Söderbergh: Nord. med. Arch. **48**: Nos. 3 and 4, 1915.
2. Beddard: Quart. J. M. **3**:329, 1909.

The accompaning table based on Kolaczek's [3] tables shows the frequency of cardiovascular and arthritic changes in the various groups.

CLASSIFICATION OF OCHRONOSIS CASES WITH ASSOCIATED LESIONS

Group	Reported by	Age, Yrs.	Sex	Pathologic Examination	Arthritis	Cardiovascular Lesions
a. Carbolic acid	Pick, 1906	47?	F	Yes	+?	+
	Pope, 1906	41	F	Yes	meager des.	
	Graeffner, 1907	59	F	No	—	—
	Reid, 1908	68	F	No	—	—
	Poulsen, 1910	55	F	No	—	+
	Poulsen, 1910	44	M	No	?	—
	Poulsen, 1910	68	F	Yes	—	+
	Beddard, 1910	60	F	No	—	—
	Andrews and Branson, 1910 (Kents), 1910	69	M	Yes	—	+
	Beddard and Plumtree, 1911	73	M	Yes	+	+
	Vogelius, 1914	63	F	No	+	—
Total, 11	Average age	52.45	8 F 3 M	5	2 + 2 ?	5
b. Alcaptonuria	Osler, 1904	57	M	No	—	+
	Osler, 1904	49	M	No	—	—
	Ogden, 1895 and 1904	45	M	No	—	—
	Allard and Gross, 1907 u 1908, Landois, 1908	46	F	Yes	+	—
	van Amstel, 1910	42	F	No	—	?
	Poulsen, 1910	56	F	No	+	—
	Poulsen, 1910	49	F	No	+	—
	Poulsen, 1910	35	M	No	—	—
	Poulsen, 1910	68	M	No	+	—
	Poulsen, 1910	61	M	No	+	—
	Kolaczek, 1910	44	F	Yes	+	—
	Kolaczek, 1910	35	F	No	—	—
	Kolaczek, 1910	30	F	No	—	—
	Poulsen, 1912	23	M	No	—	—
	Jantke, 1913	54	F			
	Umber, 1913	51	F	....	+	+
	Umber, 1913	59	M	....	+	+
	Söderbergh, 1915	42	M	....	+	—
Total, 18	Average age	47	9 F 9 M	2	9 +	2 + 1 ?
c. Probably alcaptonuria	Albrecht, 1902	47	M	Yes	—	?
	Clemens and Wagner, 1907-8	31	M	Yes	—	+
Total, 2	Average age	49	0 F 2 M	2	0	1 + 1 ?
d. Melanuria and probably alcaptonuria Total, 1	Poulsen, 1910	63	F	Yes	+	+
e. Melanuria no alcaptonuria	Hecker and Wolf, 1899	73	M	Yes	+	+
	Oppenheimer, Janney, Kline, 1916	40	M	Yes	+	+
Total, 2	Average age	56.5	0 F 2 M	2	2	2
f. No alcaptonuria and no melanuria Total, 1	Hanseman, 1892	41	M	Yes	—	+
g. Urine not obtained or not tested	Virchow, 1866	67	M	Yes	+	+
	Bostroem, 1891	44	F	Yes	+	+
	Heile, 1900	36	F	Yes	—	+
	Heile, 1900	52	F	Yes	—	+
	Wagner, 1904	67	F	Yes	—	+
	Heymann, 1913	55	M	Yes	..	+
Total, 6	Average age	53.5	4 F 2 M	6	2	6
Total cases, 41	Average age	51	22 F 19 M	19	16 + 2 ?	19 + 2 ?

3. Kolaczek: Beitr. z. Klin. Chir. **71**:254, 1910.

Moderate ochronotic pigmentation of ears, eyes and axillae; tracheal and bronchial cartilages.

Illustrating Article by B. S. Oppenheimer, M.D., and B. S. Kline, M.D., Archives of Internal Medicine, June, 1922.

In the forty-one cases of ochronosis a chronic arthritis of the larger joints or spine has been noted in sixteen. The associated arthritis has been more frequent in the ochronosis with alkaptonuria.

Cardiovascular changes have been noted in nineteen of the forty-one reported cases. These occurred in about equal frequency in cases with alkaptonuria and in cases following phenol poisoning. Not only was there extensive pigmentation of the intima and endocardium in these cases, but also not infrequently a serious chronic valvular disease.

2. *Pathologic.*—In 1866 Virchow reported on a necropsy in a male, aged 67, with an aneurysm of the ascending arch of the aorta, head

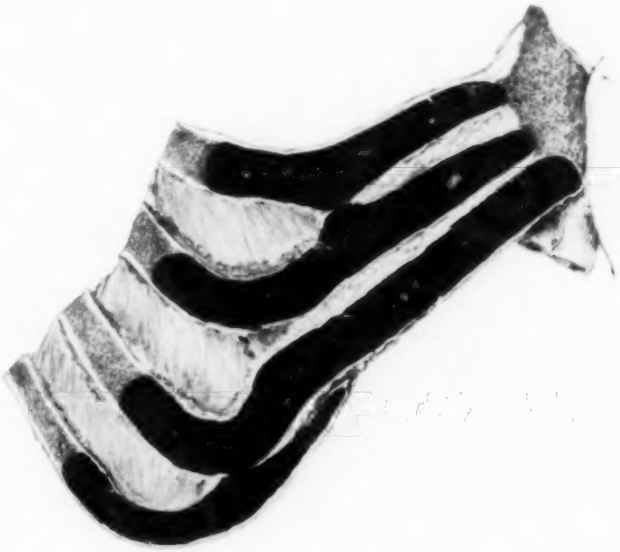

Fig. 1.—Intense ochronotic pigmentation of costal cartilages.

injury and terminal anasarca. The striking lesion, however, was the intense pigmentation of all cartilages and fibrocartilages, with pigmentation to a less extent of ligaments, tendons, perichondrium and periosteum. In this first case there was also some pigmentation of the intima of the larger vessels, especially the aorta, with intense pigmentation of the sclerotic patches in this vessel. The intensely pigmented areas were black or bluish black. The pigmentation of the tracheal cartilages was ochre colored. Histologically, the pigment everywhere was brown or ochre colored, hence the name, ochronosis. Examination of the pigment in this first case by Kühne showed an organic pigment having a definite similarity to hematin derivatives.

Virchow suggested that in ochronosis there is an imbibition from the blood of hematin derivatives occurring in areas poor in vessels and nerves but exposed to irritation. He thought that the process was analogous to the physiologic pigmentation of the rete malpighii, the hair and the choroid and depended on a similar relationship. Furthermore, he believed that there were certain conditions of the cartilages and ligaments which might be considered lower grades of ochronosis. He had occasionally observed that the semilunar plates of the knee joints in old people had a dark yellow or brown appearance and the costal and bronchial cartilages a dark yellowish brown color. In these

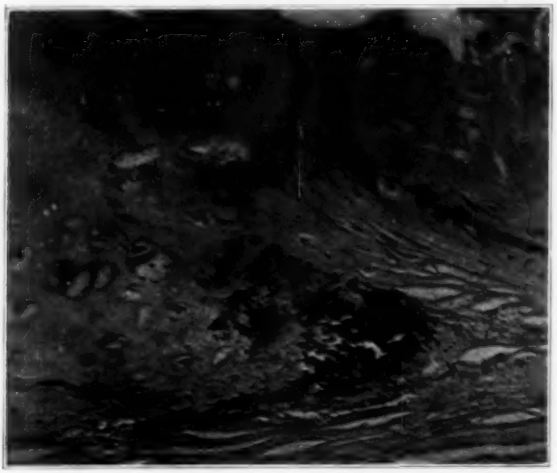

Fig. 2.—Diffuse ochronotic pigmentation of cartilaginous matrix of costal cartilage with granular ochronotic pigment in perichondrium.

instances also, the pigment was deposited in the intercellular substance and was quite homogeneous and diffuse.

Virchow, in this first case, observed changes in the larger joints, particularly the knees, similar to those in arthritis deformans. The deposition of the pigment in these irritated areas gave additional proof to him of his theory, mentioned above. In this first report, no mention of the appearance of the kidneys is made and no mention is made of granular ochronotic pigment.

In concluding his article, Virchow states: "I believe, therefore, that the case here presented, because of the intensity of the pigmentation, was only an excellent example of the more frequent ochronosis."

Hanseman [4] observed diffuse and granular ochronotic pigment in the tissues. In regard to the pigment he states that it is produced in soluble form in the body and in this form absorbed and fixed by certain tissues having but little metabolic activity and in other places changed by cells to granular pigment.

The classical paper on ochronosis is that by Poulsen,[5] who studied ten cases clinically and two after necropsy. He described the pathologic changes as follows:

In all cases one finds a yellowish or brown melanin-like pigment which at times is granular, at times stains the tissues diffusely. This pigment is deposited

Fig. 3.—Diffuse ochronotic pigmentation of intervertebral disc.

principally in the cartilages: costal, those of the air passages and larger joints. Those of the smaller joints are usually unpigmented. The pigment is also present in all the fibrocartilages, such as the intervertebral discs and in the pelvic and intersternal cartilages. The pigment deposition is less intense in the perichondrium, periosteum, tendons, fascias and joint capsules. The bones, although usually unpigmented have shown pigment in a few cases. Outside of the skeleton, the pigment is deposited as a rule only in the endocardium, intima of the larger blood vessels and kidneys; rarely in other places, such as bits of cartilage in the tonsils, in connective tissue of the lung, and

4. Hanseman: 1892.
5. Poulson: Ziegler's Beitr. z Path. Anat. **47**: 1910.

thyroid gland, in the fatty tissue about the perichondrium and in the dura mater. The pigment is frequently found in the sclerae, epidermis and in a few cases in the nails. Pigment masses have been observed in the prostate by a few observers, although the authors questioned their specific character. In the cartilage it is deposited in the matrix: the cartilage capsule, and the cells are faintly or not at all colored. Degenerated cells, however, are deeply pigmented. In the other tissues, this pigment is at times in the cells, at times between them. The pigment is excreted in the urine.

Fig. 4.—Ochronotic concretions in prostate.

REPORT OF CASE

History.—Male, aged 40, presser, admitted to Montefiore Hospital, Nov. 18, 1915.

Chief Complaints.—Lancinating pains along spinal column radiating along the lower intercostal spaces to both sides of the abdomen; slight productive cough; occasional hemoptysis; chronic constipation; general weakness; occasional spells of vomiting.

Family History.—Negative for consanguineous marriage.

Past History.—Occasional attacks of influenza. Frost bite of ears three years ago. Habits: Ten cigarets daily. Eight years before patient's admission to the hospital he was supposed to have had sugar in his urine. Seven years before admission he first noticed peculiar bluish discoloration of the cartilage of each ear.

Present Illness.—Eighteen months before admission, while bathing, he experienced sharp stabbing pains along the spinal column, extending forward along the costal spaces to both hypochondriac regions. He left the water at once and went home. The pains, however, continued to grow more and more severe until the following morning when he was unable to resume his occupation. In addition to this sharp pain he noticed stiffness of all the back muscles. He remained at home for the next six months where he was treated with no apparent relief. He then visited Mt. Clemens, Mich. On his return from Mt. Clemens he began to complain of a persistent cough accompanied by profuse greenish-yellow expectoration, blood tinged only for a period of two days,

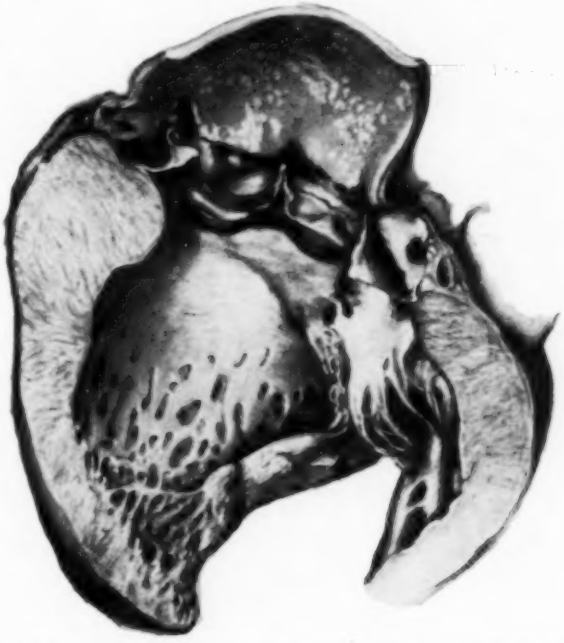

Fig. 5.—Ochronotic pigmentation of atherosclerotic plaques of aortic and mitral valves and in neighborhood of attachment of aortic cusps.

three weeks before admission. In addition he suffered with night sweats and general weakness. He lost twenty-five pounds in weight during the first year of his illness. At the time of admission, cough and loss of weight were almost negligible symptoms.

During the first twelve months of the present illness the patient was treated at various clinics. For the past three months the urine has been reddish-black; the underclothes were often stained black. Associated with this there has been marked polyuria and dysuria. The patient became frightened because of this condition and discontinued taking some white medicine which he was then receiving at the St. Paul's Tuberculosis Clinic and which he felt caused the disorder. He claims that the urinary symptoms mentioned subsided when the drug was discontinued and recurred when the drug was again taken. On being

given various drugs to smell he stated that he was positive the drug he took had the same odor as creosote.

Physical Examination.—The patient, an adult male, poorly nourished, appears to be suffering from some chronic illness. Weight, 104 pounds. Gait is very slow and careful. The sclerae of both eyes present a faint bluish tint. In addition there is a wedge shaped bluish-black area of pigmentation of the sclerae to the right of each cornea. Both ears show a peculiar leaden blue discoloration of the cartilage. The same discoloration appears to be present in the nasal cartilage on the right side. Both axillae are diffusely bluish green in color. Some of this discoloration is removable by soap and water and is apparently due to pigment from the sweat and sebaceous glands. There is a pale, brownish diffuse pigmentation of the skin of the neck and temporal regions. The fingers and toes are clubbed; nails pale, not pigmented. Chest: Supraclavicular fossae deep; clavicles exceptionally prominent. Examination of lungs shows few signs at right apex posteriorly suggestive of pulmonary

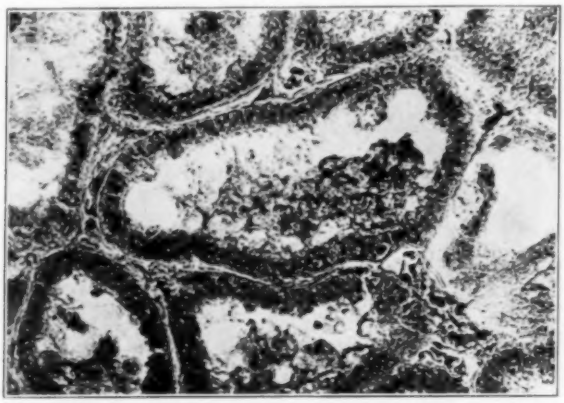

Fig. 6.—Fine ochronotic pigment granules in cells of proximal convoluted tubules of kidney.

tuberculosis. Heart: Not appreciably enlarged. The first and greater part of the second sound at the apex is replaced by a loud harsh murmur transmitted to the axilla. There is some thickening of radial arterial walls; pulse regular; good tension. Liver: Palpable 4 cm. below costal margin in right mammillary line; tender. Extremities: Reflexes increased. Vertebral column: Absolutely rigid, presenting a general bow deformity. Lumbar curve obliterated. There is a great deal of tenderness on any manipulation of either thoracic or lumbar regions of spine.

Laboratory Findings.—Sputum: negative on first five examinations. On sixth examination a few tubercle bacilli were found. Blood: hemoglobin, 80 per cent.; leukocytes, 15,000; 85 per cent. neurotrophils. Wassermann reaction of blood, negative. Urine: First specimen reddish black when voided; second specimen, when voided, light amber color, turning to yellowish black. Next two specimens were voided black. The following three specimens were smoky but on standing became black. The quantity excreted in twenty-four hours was usually 500 c.c.; specific gravity, 1.010. Albumin, marked trace. Sugar, slight reduction with Fehling's. Examination for bile and blood negative. Occasional

hyalin casts. Chemical analysis of the urine by Dr. Janney showed no homogentisic acid. On the other hand, a pigment was isolated exhibiting characteristics similar to the melanins previously obtained from the urine and tumors in cases of melanosarcoma.

Roentgen-Ray Examination of the Bones.[6]—Spine: Almost complete calcification of the intervertebral discs from the first dorsal down. The cervical spine appears practically normal. The lumbar spine shows marked lipping of the lower and upper borders of the bodies of the vertebrae (Spondylitis deformans).

Pelvic Bones: Complete calcification of the interpubic disc. Moderate amount of irregular outgrowth along the outer portions of the crests and the ossa ischii.

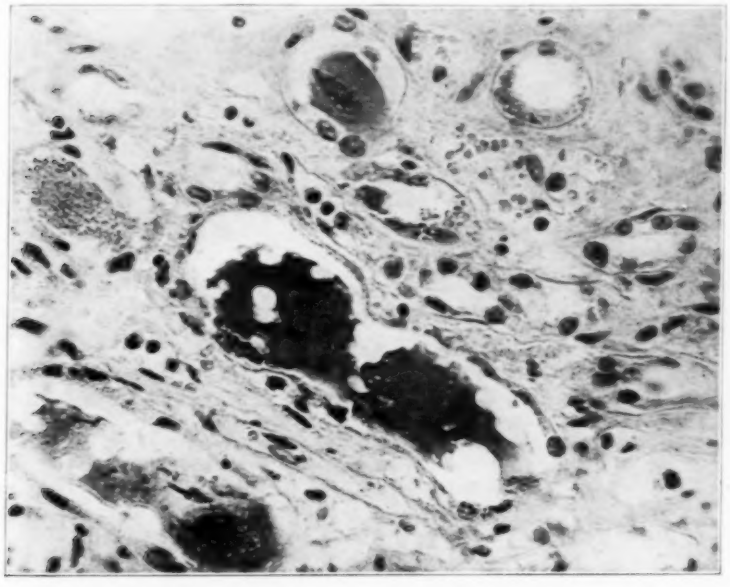

Fig. 7.—Diffuse ochronotic pigmentation of renal casts; granular ochronotic pigment granules in cells of ascending loops of Henle and collecting tubules.

Hips: Marked lipping of the upper portion of the acetabulum. Great amount of calcification around the trochanter major, with some bony excrescenses at its base.

Legs: Some calcification along the insertion of the upper portion of the membrana interossea.

Skull: Marked thinning out of both clinoid processes. Complete obliteration of the frontal sinuses.

Shoulders: The joints are free. The upper portions of the humeri show a condition such as we usually see in osteitis fibrosa; rarefaction, lack of clear demarcation between compacta and spongiosa and beginning cystic degeneration.

Clinical Course.—The patient vomited persistently, ran an irregular subfebrile temperature until the day of death when temperature rose to 103 F. A half hour after death it was noticed that the entire eyeball, exclusive of the

6. We are indebted to Dr. Th. Scholz for the roentgen-ray report in this case.

cornea, had become brownish black in color and the following day at the necropsy it was noticed that the pigment in the axillae had become much darker than during life.

Diagnosis.—The diagnosis of ochronosis in the case was readily made because of the bluish discoloration of the cartilages of the ears and the skin of the axillae; the pigmentation of the sclerae and the excretion of a dark urine becoming black on standing.

Chemical Report.[7]—Examination of the urine in this case was repeatedly negative for homogentisic acid (alkapton body). On the other hand, the pigment obtained from the urine, from a costal cartilage and from the prostate gave reactions for melanin. The pigment from these sources had similar characteristics.

Pathologic Report.—Anatomic diagnosis: ochronosis. Pigmentation of costal, tracheal, bronchial, auricular and xyphoid cartilages, intervertebral discs, aorta, endocardium, prostate, skin, sclerae, kidneys; deforming arthritis of larger joints and spine; subacute bacterial endocarditis, mitral valve; subacute glomerulitis; infarct, spleen; healed pulmonary tuberculosis; artherosclerosis of aorta, pulmonary arteries, mitral valve; pulmonary edema.

Necropsy Record (abridged).—Necropsy performed 33½ hours after death. The body is that of a considerably emaciated adult, 153 cm. in length. The skin in general is thin, sallow in appearance. There are tattoo marks on the left forearm. The nails show moderate double curvature. The skin of both axillæ, under the arms, has a purplish color. The cartilages of the ear are deep blue in the inner portion, less intensely colored peripherally. The scleræ have a faint blue tinge, except just below the cornea of each side where there is a much greater deposition of the pigment and, in addition, a wedge shaped, brownish, green-blue area about 2 x 1 cm. (These masses were not present during life, but noticed a few minutes after death.) Eyes: The right pupil is slightly larger than the left which is of about average size; both eyeballs sunken. The ears are small. The auricular cartilages through the skin appear leaden gray. There is a small nodule on the upper margin of the left ear, grape seed in size, shows grayish-pink pigmentation in the deeper portion. The external genitalia show no abnormalities, except a faint bluish discoloration on the upper surface of the glans.

(The organs removed through abdominal incision).

HEART: Somewhat enlarged, weighs 360 gm. There is considerable diminution of fat below the epicardium. The right side of the heart shows no abnormalities, except at the base of one pulmonary valve cusp and at its attachment to the artery in two places there is bluish discoloration of the intima. The left auricle is moderately dilated, the walls not thickened; the endocardium has the usual appearance except at one place above the auriculoventricular ring where there are numerous, small friable vegetations. Mitral valve—the aortic leaflet shows on its upper surface, near the auriculoventricular ring, a number of small friable, grayish vegetations. The other cusp is strikingly altered. There is a large irregular, friable mass along the line of closure and free edge, yellow in color, in part calcified; the vegetation continues down the associated chordae. The left ventricle is moderately dilated, not appreciably thickened. The papillary muscles are stretched, somewhat flattened; the endocardium thin and glistening. Aortic valve: cusps thin and delicate. At the attachment of the cusps to the ventricle and aorta there is extensive bluish black pigmentation of the endothelium over a considerable area. This pigmentation is visible also on the posterior aspect of the aortic leaflet of the mitral valve. The base of the aorta shows numerous slight elevations, due to small,

7. Dr. N. W. Janney has already published a report of the chemistry of this case. Am. J. M. Sc. **156**:59, 1918.

soft, yellow, opaque patches in the intima. The coronary vessels are not tortuous. The walls are somewhat thickened and show scattered soft yellow opaque patches in the intima; just beyond the left coronary orifice there are a few patches of bluish pigmentation of the intima. Left myocardium on section pale and flabby. Here and there are gray flecks replacing muscle. There are also gray streaks associated with the vessels. No abnormal pigmentation of myocardium.

LUNGS: The right lung weighs 690 gm. It is voluminous. The upper lobe is strikingly cushiony, especially anteriorly. The lobe also feels soggy. The pleura in general is thin and glistening, except at the apex where there are numerous puckered scars to which are attached dense fibrous tags. Below these pleural scars there is an irregular, indurated pigmented mass about the size of a robin's egg. In portions of this scarred area there are small, dry, cheesy and calcified masses. The remainder of the lobe has a watery, dull, pinkish red color, mottled with black; although crepitation is made out the air spaces contain a considerable quantity of thin fluid. Dissection of the branches of the pulmonary artery show a number of soft yellow patches in the intima. The bronchi show nothing abnormal. The hilic lymph glands not appreciably enlarged, show intense black pigmentation.

The left lung weighs 650 gm. It is voluminous. The upper lobe is inelastic, cushiony. The lower lobe feels soggy. Dissection of the vessels shows atheromatous patches in the arteries, similar to those on opposite side. The cartilaginous rings of the larger bronchi appear bluish through the mucosa. On cross section, however, they appear ochre colored. The pleura is thin and glistening everywhere. On section the upper lobe crackles. A mottled pink and black surface presents. The air spaces contain a small amount of thin fluid, especially in the lower portion of the lobe. The lower lobe on section shows a pinkish-red moist surface. Thin fluid exudes in considerable quantity from the air spaces.

LIVER: Weighs 1,750 gm.; shows no macroscopic abnormalities.

SPLEEN: Weighs 350 gm.; measures 16 x 9 x 4 cm. About twice average size. It has the average consistency. The capsule is thin. Toward the upper pole there is a triangular area with sides 2½ cm. and base 1¾ cm., yellow in color, opaque, depressed a few millimeters below the general level. On section of the spleen a striking picture presents. The surface is soft and pasty, red in color. Scattered throughout the pulp are numerous small gray areas about pinhead in size. The pulp scrapes off readily on the knife. The trabeculae are increased in number, but not in size. The depressed area noted on the surface is found to be a part of a typical wedge shaped infarct, homogeneous throughout, dry, yellow and opaque, except at the apex where for a considerable distance the tissue has a decidedly bluish color.

PANCREAS AND SUPRARENALS: No appreciable abnormalities.

KIDNEYS: The kidneys together weigh 500 gm. Both are apparently alike. Each measures 12½ x 8 x 6 cm. Each moderately enlarged. The capsule strips readily, showing a smooth surface in which the veins are prominent. In addition, innumerable pinpoint and larger bluish black spots are seen. On section, a striking picture presents. The cortex is quite uniform in width, averages from 8 to 9 mm., has a watery gray-reddish appearance, streaked and dotted with brownish and bluish pigmentation. The striations are not very distinct but are fairly regular. The glomeruli are inconspicuous. Brownish and bluish pigment streaks and dots are quite extensive in the medulla and most striking in the papillae.

BLADDER: The bladder of average size, the walls of average thickness, contains turbid urine. The mucosa is pale except for a few scattered areas of injection, especially marked in the trigone. The prostatic urethra presents a striking picture; there are stony, bluish pigment masses varying in size from

pinpoint to grape seed; in some places entirely covered by mucosa, elsewhere only partially covered. There is no injection about these masses.

PROSTATE: The prostate is of average size and consistency. On section it contains a number of bluish black pigment masses varying in size from pinpoint granules, to several as large as peas. The nodules are stony in consistency.

SEMINAL VESICLES: The seminal vesicles are thin walled, not pigmented.

VESSELS: The aorta is elastic, the walls of average thickness, the circumference in upper thoracic portion 5 cm. There are numerous rather broad longitudinal yellow opaque masses in the intima throughout the length of the aorta. Just at the commencement of the thoracic portion there is an atherosclerotic plaque which shows considerable bluish black pigmentation over a surface of about a square centimeter. In addition there is a slight diffuse bluish pigmentation of the intima for a distance of 4 cm. in the neighborhood of the intercostal vessels.

NECK ORGANS: Only the lower part of the trachea was removed. This shows a pale, thin mucosa through which the cartilaginous rings have a decidedly bluish color. This is true also of the bronchi. On cross section, the pigmentation of the cartilaginous rings is found to be central; in some, it is most marked on the convex portion. The outer rim of pigmentation has a bluish cast; the deeper portions are brown.

INTESTINES: There is some apparent hyperplasia of the lymphoid tissue of the small and large intestines. In the colon there are also a number of irregular areas from 1 to 2 cm. square, having a smooth, pearly scarred appearance with thin brown pigmented periphery, suggesting healed ulcers.

SPINE: The bodies of the lumbar vertebrae are considerably flattened, the intervertebral discs are narrower than normal and almost bony in consistency; the striking change of the discs is the diffuse, intense bluish black pigmentation. The anterior ligament of the spine macroscopically shows no pigmentation.

THORAX: The lower portion of the sternum and adjoining costal cartilages and ribs were removed through the abdominal incision. The costal cartilages present a striking picture; they are hard and everywhere show an intense bluish black pigmentation. The removed ribs and portions of sternum, however, show no apparent pigmentation.

Owing to the fact that permission was granted for a partial necropsy only, the larger joints of the body could not be investigated.

Roentgenograms of all the joints were made, however, and showed changes characteristic of arthritis deformans of the spine with well marked changes of the larger joint (hip and knee) especially about the attachments of the capsules. The smaller joints showed very little change. (Dr. Th. Scholz).

Histologic Report.—TRACHEAL CARTILAGES: Sections show diffuse pigmentation of the matrix about the cartilage cells and clumps of fine brown granules in the perichondrium. Most of the pigment is deposited in the matrix and immediately surrounding the cartilage cells.

COSTAL CARTILAGE: Section shows diffuse brown pigmentation of the matrix. In addition, a number of degenerated cartilage cells contain diffuse and granular brown pigment. The perichondrium is pigmented in places; the pigment present in the form of small brown granules.

INTERVERTEBRAL DISC: Intervertebral disc considerably narrower than average, in part composed of fibro-cartilage, in part there are large cartilaginous like plaques. In the matrix of these latter there is diffuse brown pigmentation. In the fibrous portion near the anterior ligament there is considerable granular brown pigmentation.

AORTA: Section shows a few atherosclerotic patches in the intima, associated with which there is a considerable amount of extracellular brown pigment in diffuse and small granular form.

PROSTATE: The architecture in general is normal. There are rather numerous corpora amylacea in the glands. These vary in appearance. A few show a large amount of diffuse brown pigment in the central portions, the peripheral portions unpigmented, stained pink (eosin). Various stages of pigmentation are seen, including large and small corpora amylacea, diffusely and homogeneously brown stained. About a few of the glands containing the pigmented corpora, there are accumulations of round cells, principally mononuclears. A number of the glands containing these masses show partial or complete absence of the epithelium.

ENDOCARDIUM: This is considerably thickened. To it is attached a large thrombus mass, composed of strands of fibrin, red cells and fragmented leukocytes. Another section shows an area of the thrombus in which there is beginning calcification. In the deeper layers of the endocardium there are small masses of extracellular brown pigment in the form of fine granules. Section stained by Gram-Weigert stain shows in the outer portions of the thrombus numerous small round diplococci, many in small chains.

KIDNEY: There is some distortion of the striations. In areas there is an increase in the interstitial connective tissue; in some of these areas there is an accumulation of round cells in considerable number. In a number of these areas and also elsewhere the glomeruli have an altered appearance. The glomerular tuft is adherent to the capsule in one or more places. In places the glomerular sac contains amorphous, pink stained material and a few large mononuclear cells. In a very few glomeruli there are a large number of mononuclear cells within the sac, all filled with fine, brown pigment granules. The neighboring convoluted tubules also show a deposition of a large amount of granular brown pigment in the epithelium. In sections stained with silver nitrate, the ochronotic pigment is found in the form of very fine granules in cells of the proximal convoluted tubules and in the form of larger granules in the intact and desquamated cells of many of the ascending limbs of the loops of Henle and the various collecting tubules. The cells of the distal convoluted tubules contain the granular pigment in moderate amount. In general the pigment in the lumina of the tubules is diffuse. In places, however, desquamated cells containing granular pigment are present. In addition to these changes, a number of the tubules contain nucleated cells mostly polymorphonuclear leukocytes and in places the interstitial tissue shows accumulations of similar cells. In addition, in the interstitial tissue of cortex and medulla there are scattered large mononuclear cells containing brown pigment.

SPLEEN: Section shows a very large, triangular area of homogeneously pink stained amorphous material in which phantoms of former splenic structures are seen. In addition to the pink stained material there is, in places, some nuclear dust and more strikingly there are clumps of intra and extra cellular brown pigment. The greatest deposits of the pigment are found immediately surrounding this infarct, in the new formed connective tissue, which is present as a fairly wide band; the remainder of the section shows normal looking trabeculae and vessels. The malpighian bodies are very small, and lessened in number. There is, however, an increase in the nucleated cells of the pulp. There are numerous plugs of cocci in the splenic capillaries. Another section of the spleen shows the presence of a number of clumps of yellowish brown pigment scattered throughout the infarct. In the center of this infarct there is the remains of a large blood vessel plugged with homogeneous, pink stained material.

LIVER: This shows considerable engorgement of the blood vessels in the central portions of the lobules. There is a striking increase in the number of nucleated cells in the capillaries. In one capillary a very large clump of cocci is seen.

Michrochemical Report.—In sections stained by Nishimura's method, the ochronotic pigment, diffuse and granular, does not show the reaction for iron.

In formalin-fixed material, the diffuse ochronotic pigment is stained orange red by neutral red (1 per cent. aqueous solution, three hours at 56 C.); the granular ochronotic pigment, however, is not stained by this method.

The granular ochronotic pigment behaves microchemically very much like the pigment of brown atrophy. Both are decolorized by (1) potassium permanganate, sodium sulphite, oxalic acid. (Potassium permanganate, 1/4 per cent. solution, one half hour; equal parts of oxalic acid and sodium sulphite, 1 per cent. solution, 10 minutes.); (2) surgical solution of chlorinated soda (from 15 to 30 minutes), and (3) bichromate sulphuric acid solution (potassium bichromate, 10 gm.; sulphuric acid concentrated, 12 c.c.; water, 100 c.c.) one half hour. Both the diffuse and the granular ochronotic pigment are stained brownish black by silver nitrate (fresh 2 per cent. solution silver nitrate, twenty-four hours at 56 C.). The form and distribution of the pigment are best demonstrated by this method.

SUMMARY OF FORTY-FIRST CASE

Clinical.—The diagnosis of ochronosis was made in this case because of the bluish discoloration of the cartilages of the ears and skin of the axillae; the pigmentation of the sclerae and the excretion of a dark urine becoming black on standing. In addition the patient had a deforming arthritis of the spine and larger joints and a mitral endocarditis: complications frequently present in ochronosis.

Chemical.—Examination of the urine was repeatedly negative for alkapton body. The pigment obtained from the urine, from a costal cartilage and that from the prostate of the case gave the reactions for melanin. The pigment from these three sources had similar characteristics. The chemical findings are in accord with the belief that ochronosis is dependent on a disordered metabolism of phenol derivatives.

Pathologic.—As in the cases previously reported, the cartilages (costal, tracheal, bronchial, auricular and xyphoid), and fibrocartilages (intervertebral discs) are deeply pigmented (bluish black). Large stony masses of bluish pigmentation are found in the prostate and prostatic urethra. The kidneys likewise show extensive pigmentation. The endocardium, intima of the aorta and coronary arteries, skin and sclerae are less intensely pigmented. The pigment is not deposited in any quantity in intact intima and endocardium but in areas of degeneration in these structures, however, macroscopic deposits occur. Diffuse ochronotic pigment is present in albuminous masses (renal casts) and concretions (corpora amylacea of prostate). Fine pigment granules are present in the epithelium of proximal convoluted tubules, and coarser granules are present in the cells of the ascending loops of Henle, distal convoluted tubules and the collecting tubules.

The pigment is predominatingly diffuse in the matrix of the cartilage and fibrocartilage and when associated with albuminous masses and concretions. It is predominatingly granular in perichondrium, periosteum, tendons, fascias, connective tissue and in certain

renal cells. It is present in diffuse and granular forms in injured and degenerated areas.

The histologic picture in the kidney sections suggests excretion of the pigment by the cells of the proximal convoluted tubules. The picture likewise suggests a partial reabsorption of the fine pigment by the cells of the loops of Henle, distal convoluted tubules and collecting tubules, and a transformation of the pigment into a more granular form. The form and distribution of the pigment is demonstrated best in histologic sections stained with silver nitrate.[8]

We are indebted to Mrs. H. G. Friedman for her kind assistance in preparing this paper.

8. Other references bearing on this subject are: Poulsen: Literature to 1910, Beitr. z. path. Anat. u. z. allg. Path. **48**:346, 1910; Literature to 1912, Münch. med. Wchnschr. **59**:364, 1912; Beddard and Plumtree: Quart. J. M. **12**:505, 1911; Umber and Bürger: Deutsche. med. Wchnschr. **48**:2337, 1913; Jantke: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:617, 1913; Heymann-Giessen: 1913; Vogelius: Hospital tidende. 1164, 1914; Sprunt: Ochronosis, Nelson's Living Medicine **3**:211, 1920; Howard: Ochronosis, Oxford Medicine **4**:223, 1921.

AIDS TO BASAL METABOLIC RATE DETERMINATIONS *

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This paper contains charts and tables so arranged as to facilitate considerably the otherwise laborious calculation of basal metabolism values. They are in such form as to be useful in calculating basal metabolic rate from data obtained with any form of apparatus. They are intended primarily for use in connection with determinations made by some method involving the use of a Haldane gas analysis apparatus. Such methods in common use are either that described by Boothby and Sandiford [1] in which the expired air is collected in a large spirometer, or the method of Douglas [2] in which a rubber bag is used for this purpose and the volume of its contents measured with a meter.[3] In either of these methods the gasometric data include figures for volume, temperature, pressure, and carbon dioxid and oxygen content of the expired air. From these are to be computed the respiratory quotient and oxygen consumption at standard conditions of temperature and pressure. The figure for oxygen consumption, when mulfiplied by the calorific value of oxygen, gives a figure for calory production.

Certain instruments, as for instance the Benedict portable apparatus,[4] read the uncorrected oxygen consumption directly and a respiratory quotient of 0.82 corresponding to a calory value per liter for oxygen of 4.825 is assumed.

In calculating basal metabolic rate, the patient's calory production is compared with the normal. It is generally customary to use as standards the figures of Aub and DuBois, giving the normal calory production per square meter of body surface. The body surface of the patient is calculated from the height weight chart of DuBois. There are also available the standard multiple prediction tables of

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* From the Laboratory of the Henry Phipps Institute of the University of Pennsylvania.

1. Boothby, W. M., and Sandiford, I.: Laboratory Manual of Basal Metabolic Rate Determination, Philadelphia, 1920.
2. Carpenter, T. M.: Carnegie Inst. Wash. Pub. No. 216, 1915, p. 67.
3. Newcomer, H. S.: J. Biol. Chem. **47**:489, 1921.
4. Benedict, F. G., and Collins, W. E.: Boston M. & S. J. **183**:449, 1920.

Benedict, as well as certain other data, applying to children.[5] In its simplest form the calculation is laborious and when it is desirable to obtain the additional information to be had by the use of a Haldane apparatus, the computation involves the expenditure of an appreciable amount of time and gives opportunity for the appearance of numerical errors.

The use of the charts and tables at the end of this paper restrict this labor to the performance of a simple algebraic sum. In several instances they condense hitherto available tables of many pages to a single sheet. There follows a description of their derivation and then directions for their use with examples.

Derivation of Formulae and Charts.—Charts 1 and 2 are intended for use with the Haldane gas analysis apparatus and are used to obtain hourly calory production. Chart 2 corrects the gas volume to standard conditions of temperature and pressure and includes a correction for water vapor.

Apparatus such as that of Benedict which reads oxygen consumption directly, that is, which reads the diminution in oxygen volume of a closed system including the patient's respiratory tract, does not involve a correction for water vapor. The observed diminution in oxygen volume is, therefore, to be reduced to standard conditions by a factor which does not include a correction for saturation with water vapor. Chart 3 supplies the logarithm of this correcting factor. The hourly calory production may be obtained by multiplying the oxygen consumption in c.c. per minute by 0.2895 (log. $0.2895 = \overline{1}.4617$). The other charts and tables have to do with basal metabolism standards. In the computation of the charts and tables five figure logarithms were used except that in the case of Chart 1 it was necessary to use seven place tables.

Chart 1 has as abscissae the reading of the Haldane buret after absorption of carbon dioxid, it being assumed that the Haldane buret was filled in the first place to the 10 c.c. mark at atmospheric pressure. The ordinates are the Haldane readings after carbon dioxid and oxygen absorption. It is further assumed that these readings are corrected for any calibration error which the Haldane buret may have, and that the patient breathes outside air. This may be either through a tube out the window, or, if the room can be well aired, it suffices to leave the window open for some time before starting. The chart has two families of lines; the horizontal ones give, by interpolation between them, the value of the respiratory quotient, volume of carbon dioxid production divided by volume of oxygen absorption. The more vertical lines are the logarithms of factors, portion of oxygen absorbed times the calorific value of one liter of oxygen at the equivalent respiratory quotient. The value of the logarithm of this factor corresponding to any pair of Haldane readings is obtained by interpolation between this family of lines.

5. Carpenter, T. M.: Carnegie Inst. Wash. Pub. No. 303, 1921.

TABLE 1.—Barometer Correction for Change in the Value of Gravity with Latitude to Be Subtracted from or Added to the Observed Height of the Barometer Before Going to Charts 2 or 3

Latitude	0° 90°	5° 85°	10° 80°	15° 75°	20° 70°	25° 65°	30° 60°	35° 55°	40° 50°	45° 45°
710 mm. Subtract mm. Add	1.84	1.81	1.73	1.59	1.41	1.18	0.92	0.63	0.32	0.00
760 mm. Subtract mm. Add	1.97	1.94	1.85	1.70	1.51	1.27	0.98	0.67	0.34	0.00

The correction varies with the height of the barometer. To correct for altitude subtract 0.14 mm. of mercury for every one thousand meters above sea level. To correct for the capillary depression of the mercury column see the text. Combine all of these corrections into one and use only if significant.

TABLE 2.—Logarithms of Standard Reciprocal Normal Basal Metabolism Factors for Children 17 Years of Age and Under Referred to Weight in Pounds. (Benedict)

Wt.	Boys	Girls	Wt.	Boys	Girls	Wt.	Boys	Girls	Wt.	Boys	Girls
6	$\bar{1}.264$	$\bar{1}.274$	36	$\bar{2}.408$	$\bar{2}.522$	66	$\bar{2}.323$	$\bar{2}.360$	96	$\bar{2}.270$*	$\bar{2}.268$
8	.106	.093	38	.485	.510	68	.320	.351	98		.287
10	$\bar{2}.996$	$\bar{2}.974$	40	.472	.498	70	.318	.344	100		.286
12	.908	.885	42	.455	.487	72	.311	.337	102		.285
14	.835	.813	44	.444	.475	74	.304		104		.284
16	.774	.758	46	.433	.463	76	.297	.320*	106		.283
18	.724	.712	48	.422	.451	78	.291		108		.282
20	.682	.679	50	.411	.440	80	.285	.305*	110		.281
22	.645	.649	52	.400	.430	82	.280		112		.280
24	.614	.621	54	.390	.419	84	.274	.295	114		.279
26	.589	.595	56	.379	.408	86		.294	116		.278
28	.567	.572	58	.368	.399	88		.292	118		.277
30	.547	.564	60	.358	.389	90		.291	120		.276
32	.529	.549	62	.350	.379	92		.290	124		.274
34	.513	.536	64	.342	.371	94		.289	128	.260*	.272

The figures are the logarithms of reciprocal total calories per hour of children weighing from 6 to 128 pounds. The figures are calculated from data by Benedict and Talbot, and Benedict and Hendry. The numbers with an asterisk are not due to these authors but are supplied as probable values in order to make the table complete.

TABLE 3.—THREE FIGURE LOGARITHMS

	0	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9
1	000	041	079	114	146	176	204	230	255	279	4 3 3 3 2	8 7 6 6 5	12 10 9 8 7	16 13 12 11 10	20 17 15 13 12	24 20 18 16 14	28 24 21 18 16	32 27 24 21 19	36 30 26 23 21
2	301	322	342	362	380	398	415	431	447	462	2 2 2	4 4 3	6 5 5	8 7 6	10 9 8	12 11 9	14 12 11	16 14 12	18 16 14
3	477	491	505	518	531	544	556	568	580	591	2 1	3 2	4 4	6 5	7 6	8 7	10 8	11 9	12 10
4	602	613	623	633	643	653	663	672	681	690	1	2	3	4	5	6	7	8	9
5	699	708	716	724	732	740	748	756	763	771	1	2	2	3	4	5	6	6	7
6	778	785	792	799	806	813	820	826	833	839	1	1	2	3	3	4	5	5	6
7	845	851	857	863	869	875	881	886	892	898	1	1	2	2	3	4	4	5	5
8	903	908	914	919	924	929	934	939	944	949	1	1	2	2	3	3	4	4	5
9	954	959	964	968	973	978	982	987	991	996	1	1	1	2	2	3	3	4	4
	0	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9

The figures of the table are the mantissae of two figure numbers. The columns at the right are the proportional parts to be added to the mantissae to make them the mantissae of three figure numbers. The characteristic of the lograrithm is the number less one of integral digits in the number.

TABLE 4.—THREE FIGURE ANTILOGARITHMS

	0	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9
0	100	102	105	107	110	112	115	117	120	123	0	1	1	1	1	2	2	2	2
.1	126	129	132	135	138	141	145	148	151	155	0	1	1	1	2	2	2	3	3
.2	158	162	166	170	174	178	182	186	191	195	0	1	1	2	2	2	3	3	4
.3	199	204	209	214	219	224	228	234	240	245	1	1	2	2	3	3	4	4	5
.4	251	257	263	269	275	282	288	295	302	309	1	1	2	3	3	4	5	5	6
.5	316	324	331	339	347	355	363	371	380	389	1 1	2 2	2 3	3 4	4 4	5 5	5 6	6 7	7 8
.6	398	407	417	427	437	447	457	468	479	490	1 1	2 2	3 3	4 4	5 5	6 7	7 8	8 9	9 10
.7	501	513	525	537	550	562	575	589	603	617	1 1	2 3	4 4	5 5	6 7	7 8	8 10	10 11	11 12
.8	631	646	661	676	692	708	724	741	759	776	1 1 2	3 3 4	4 4 5	6 6 7	7 8 9	9 10 11	10 11 12	12 13 14	13 14 16
.9	794	813	832	851	871	891	912	933	955	977	2 2 2 2	4 4 4 5	6 6 6 7	8 8 8 9	9 10 11 11	11 12 13 13	13 14 15 16	15 16 17 18	17 18 19 20
	0	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9

The figures of the table are the numbers corresponding to two figure mantissae. The columns at the right are proportional parts to be added to the numbers to make them numbers corresponding to three figure mantissae. The characteristic of the logarithm is omitted in going to the table. The number is to be pointed off so as to have a number of integral digits equal to the characteristic plus one. If the characteristic is negative the number is to be prefaced by a number of decimal zeros equal to the characteristic plus one (with regard to sign).

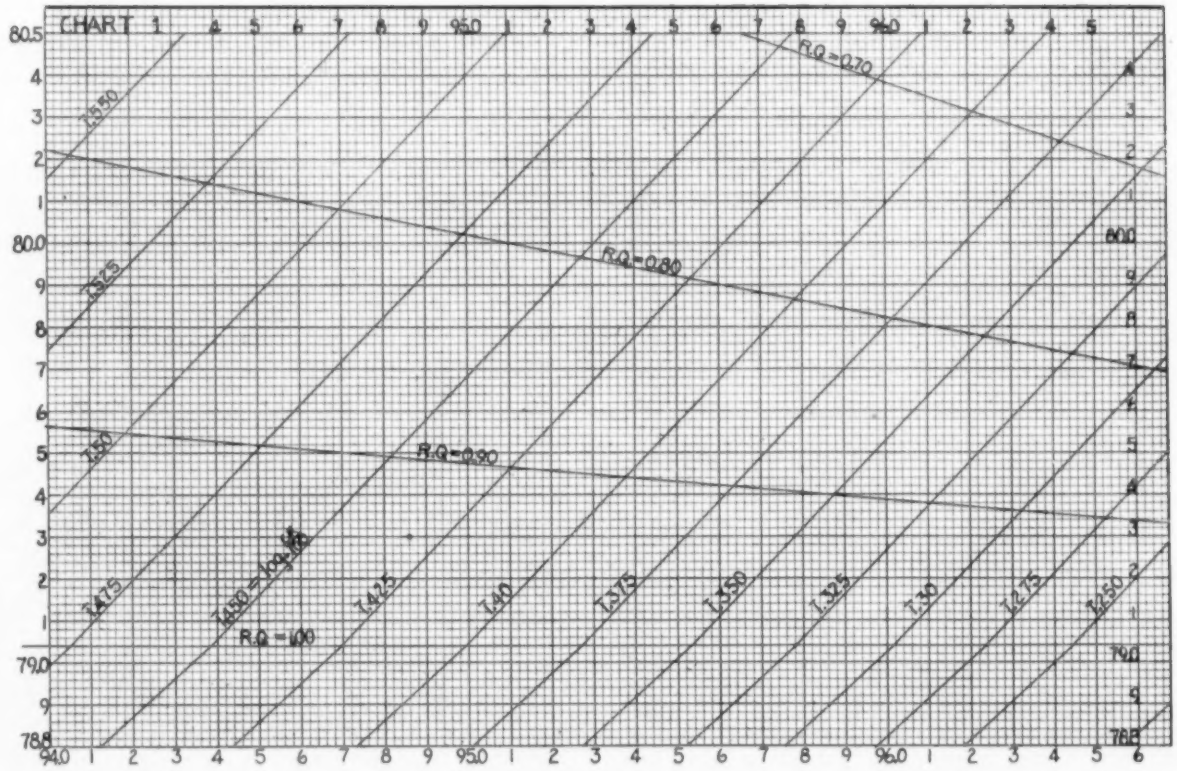
CHART
R.Q.=0.70
R.Q.=0.80
R.Q.=0.90
R.Q.=1.00
1.450 = 100%O2
1.500
1.475
1.425
1.400
1.375
1.350
1.325
1.300
1.275
1.250
80.5
80.0
79.0
78.8
94.0
95.0
96.0

Chart 1A.

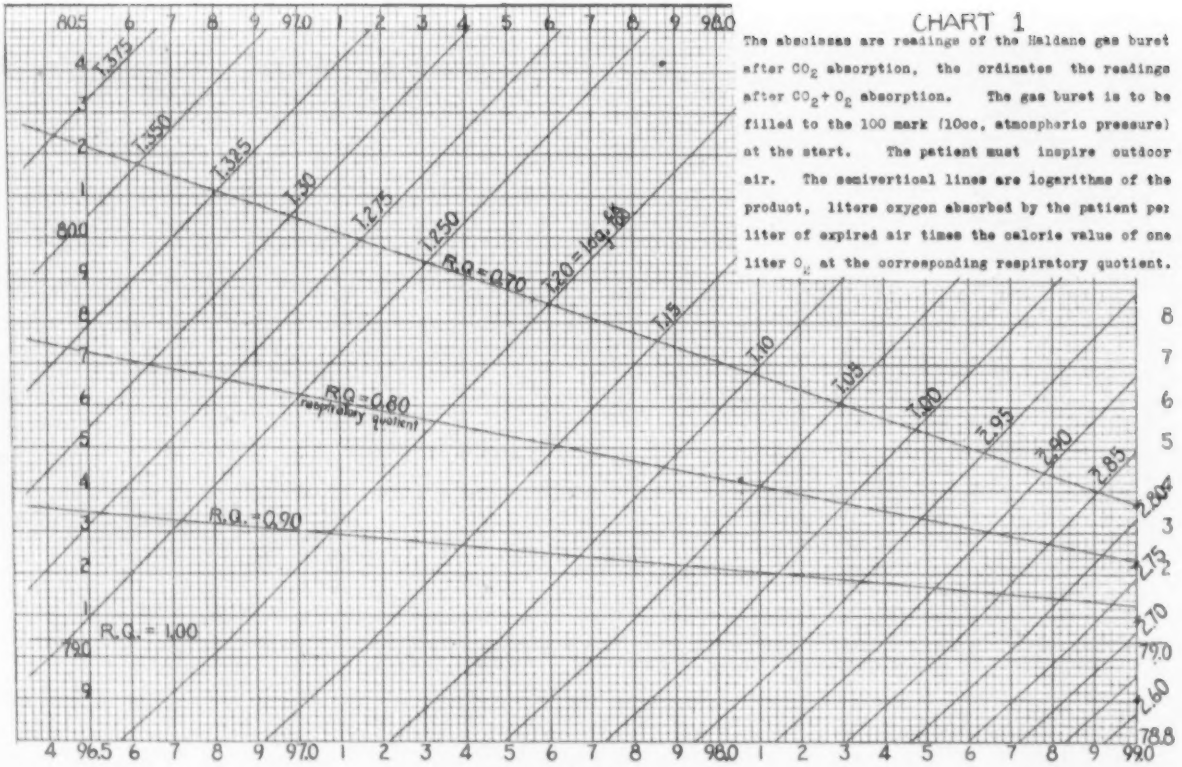
CHART 1
The abscissas are readings of the Haldane gas buret after CO_2 absorption, the ordinates the readings after $CO_2 + O_2$ absorption. The gas buret is to be filled to the 100 mark (10cc, atmospheric pressure) at the start. The patient must inspire outdoor air. The semivertical lines are logarithms of the product, litere oxygen absorbed by the patient per liter of expired air times the calorie value of one liter O_2 at the corresponding respiratory quotient.
1.375
1.350
1.325
1.30
1.275
1.250
R.Q.=0.70
1.20
1.15
1.10
1.05
1.00
2.95
2.90
2.85
2.80
2.75
2.70
2.60
R.Q.=0.80
respiratory quotient
R.Q.=0.90
R.Q.=1.00

Chart 1B.

The derivation of these two families of lines is as follows:

Let x = reading of Haldane after CO_2 absorption
= 100 — CO_2 percentage in expired air
y = reading of Haldane after $CO_2 + O_2$ absorption
(1) = 100 — ($CO_2 + O_2$) percentage in expired air
= nitrogen percentage in expired air

If 20.93 be the value taken for the oxygen percentage in the inspired air, outside air, and 0.03 the carbon dioxid percentage, then 79.04 is the nitrogen and other inert gas percentage in the inspired air. The fraction $\frac{y}{79.04}$ represents the change in volume of the air due to alveolar gas exchange, and the oxygen absorption in per cent. is given by

$$(2) \qquad \frac{20.93\,y}{79.04} - O_2 = K$$

where O_2 is the oxygen percentage of the expired air. From (1) and (2)

$$\frac{20.93\,y}{79.04} + y - 100 + CO_2 = K$$

or

$$(3) \qquad \frac{99.97}{79.04}\,y - x = K$$

These are a family of lines of slope $\frac{79.04}{99.97} = .790637$ giving constant oxygen absorption K. The values of the calorific equivalent, C, of one liter of oxygen for the respiratory quotients 0.707 to 1.00 as tabulated by Lusk[6] are given with an error of less than one part in one thousand by the formula

$$R.\,Q. = 0.813\,C - 3.103$$

But by definition $R.\,Q. = \frac{100 - x - 0.03}{K}$

Therefore

$$\frac{100 - x - 0.03}{K} = 0.813\,C - 3.103$$

$$C = \frac{100 - x - 0.03}{0.813K} + \frac{3.103}{0.813}$$

$$(4) \qquad CK = \frac{100 - x - 0.03}{0.813} + \frac{3.103}{0.813}K$$

substituting (3) in (4)

$$CK = \frac{100 - x - 0.03}{0.813} + \frac{3.103}{0.813}\left(\frac{99.97}{79.04}y - x\right)$$

$$CK = 4.8274y - 5.04674x + 122.9643$$

= per cent. oxygen absorbed times its calorific value per liter.

This family of lines is plotted for values of CK whose logarithms are 0.60, 0.65, 0.70, etc., to 1.55. K is the number representing per cent. oxygen absorbed by the patient. The fraction $\frac{K}{100}$ is, therefore, a number which multiplied by the expired volume is the oxygen absorbed by the patient. $\frac{CK}{100}$ is its calorific value and the logarithms of $\frac{CK}{100}$ instead of the above logarithms of CK are assigned as signatures to the family of lines, namely, $\overline{2}.60, \overline{2}.65, \overline{2}.70, \ldots$ to $\overline{1}.55$.

6. Lusk, G.: The Science of Nutrition, Ed. 3, Philadelphia, 1919, p. 61.

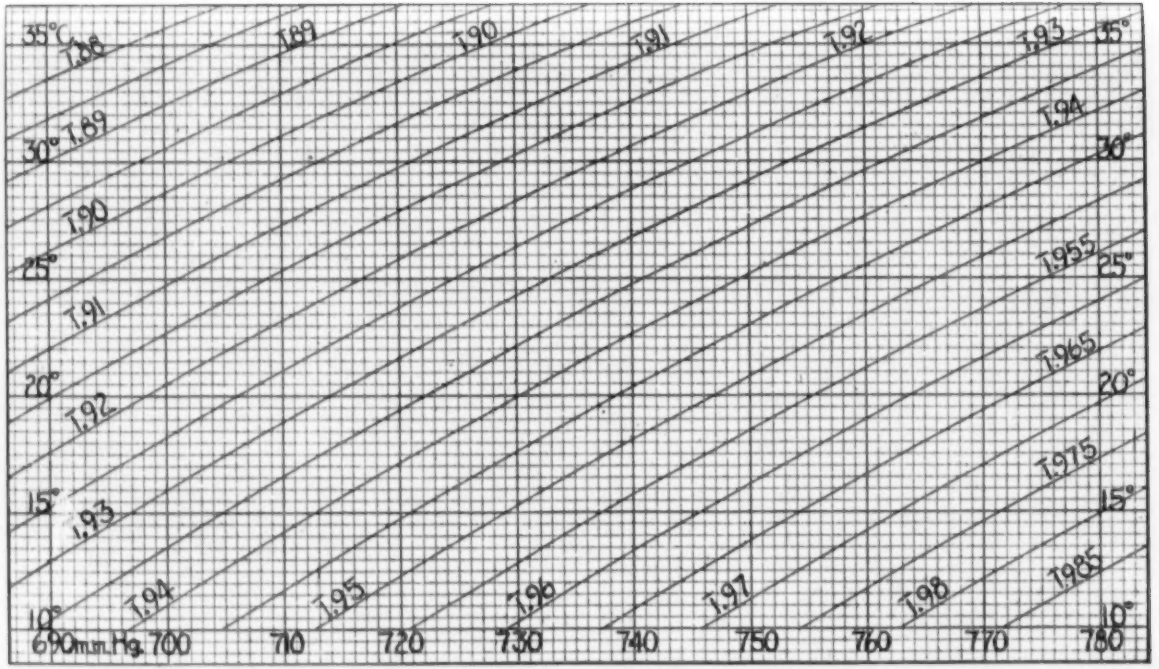

Chart 2.—The ordinates are temperatures centigrade and the abscissas observed barometric pressures in mm. of mercury. The lines are logarithms of the factor reducing observed volume of water vapor saturated air to 0 C., dry, 760 mm. sea level and latitude 45 degrees, including a reduction of the barometer readings, brass scale, to 0. C. Log $\frac{\text{p — vap. ten. — scale correction}}{760} \times \frac{1}{1+0.00367\ t}$

For the other corrections which may be advisable see Table 1.

When the respiratory quotient is greater than unity the heat production is due to the oxygen consumption plus the heat produced in the transformation of the carbohydrate into fat during which the extra carbon dioxid was produced. The heat value of this transformation, according to Lusk, is 0.8 calories per liter carbon dioxid. For readings below the line RQ = 1 carbohydrate is being burned at a rate producing an oxygen percentage absorption corresponding to a CK line of the reading where C is the 5.047 of RQ = 1. In addition, carbohydrate is being converted into fat with a carbon dioxid percentage production equal to the difference between x where the CK line crosses RQ = 1, and the observed x. To this additional CO_2 there corresponds a calory production of 0.8 per liter. In order to calculate the total calory factor, we may draw a line of the family K = constant through the point given by the intersection of the CK line and RQ = 1. If this be considered as a new CK line it is a line along which neither C nor K changes. The new calory factor line is then one passing through the CK, RQ point and having a slope sufficiently steeper than the constant K line to make an observed point on the constant K line and one x unit smaller than the x of the CK, RQ point lie 0.8 of the distance between the new line and a next parallel one having a value one unit larger. Therefore, below the line RQ = 1, the constant calory factor lines bend slightly, as shown in the chart, and for readings below the line RQ = 1, the patient is putting on fat at the moment in question.

Chart 2 is computed from data by Kaye and Laby.[7] It is a family of curves giving by interpolation the logarithms of the factor reducing the observed air volume to 0 C., 760 mm. of mercury at latitude 45 degrees and sea level, dry, together with a correction to 0 C. of the mercury columns and brass scale. The corrections for brass and glass scales are nearly the same. At 10 C. the correction for glass to be subtracted is 0.07 mm., and at 34 C., 0.25 mm. greater than that correction for brass which has been subtracted from the barometric height in computing the curves. The table does not include barometer corrections due to the change in the value of gravity with latitude and height above sea level. If it is desired to correct for latitude, add or subtract from the observed barometer the figures of Table 1 before reading from the chart. The change in gravity due to altitude is such that for every one thousand meters above sea level one should subtract from the observed barometer approximately 0.14 mm. of mercury. It may be proper in addition to correct for the capillary depression of the mercury column. This correction is zero if both mercury levels have the same cross section, as is the case with the usual all glass barometer. For barometers having a mercury reservoir the figures to be added to the barometer reading for bores of 4, 5, 6, 7, and 8 mm. are, respectively, 1.2, 0.7, 0.4, 0.25, and 0.2 mm., provided the height of the meniscus itself is 0.6 mm. For heights of the meniscus greater than this and up to 1.6 mm. these figures are to be increased uniformly per 0.2 mm. of height respectively by 0.4, 0.25, 0.2, 0.15, and 0.1 mm. These corrections for gravity and capillary depression may of course be determined at any place once for all and combined into one single correction for the barometer.

Table 2 is derived from data by Bendict and Talbot[8] and Benedict and Hendry.[9] It gives the logarithms of the reciprocal of the total number of calories produced per hour by children seventeen years of age and under. The numbers are computed from the tables of these authors. The numbers with an asterisk are supplied to make the table complete, the two for girls being easily inserted by interpolation. The additional numbers for boys cannot be supplied with the same assurance. There should be a continued gradual decrease in the

7. Kaye, G. W. C., and Laby, T. H.: Table of Physical and Chemical Constants, Ed. 2, London, 1916.

8. Benedict, F. G., and Talbot, F. B.: Carnegie Inst. Wash Pub. No. 302, 1921, p. 206.

9. Benedict, F. G., and Hendry, M. F.: Boston M. & S. J. **184**:329, 1921.

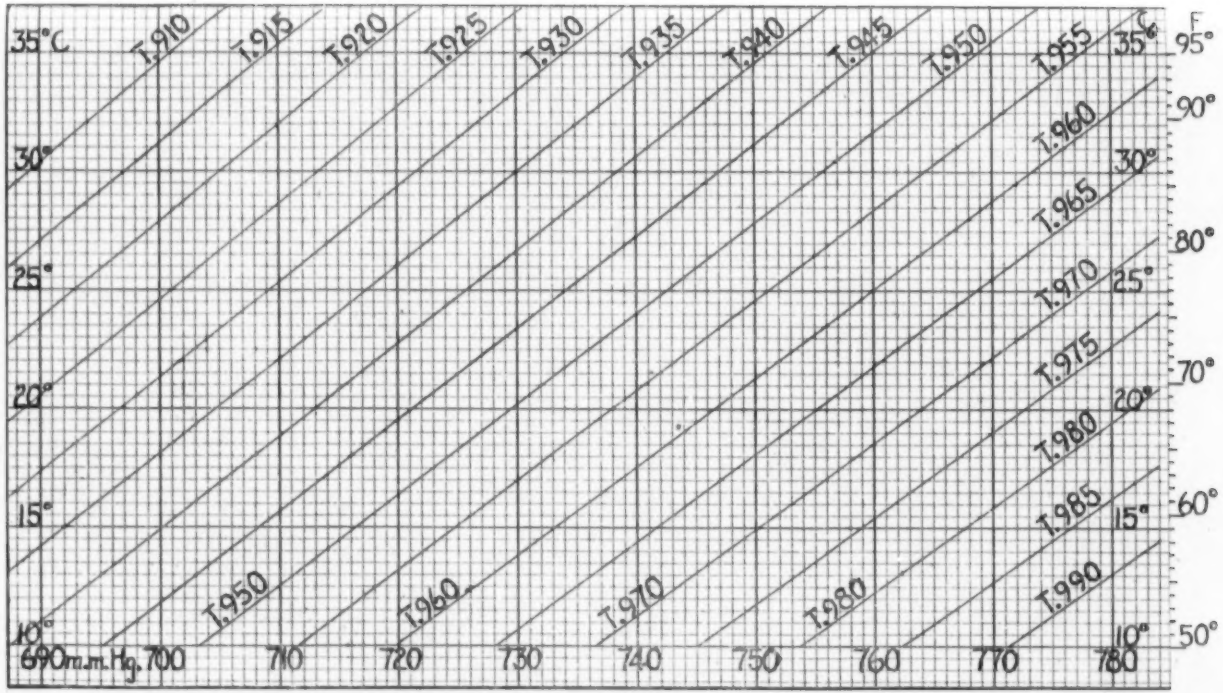

Chart 3.—The ordinates are temperatures centigrade and the abscissas observed barometric pressures in mm. of mercury. The lines are logarithms of the factor reducing observed volume of dry air to 0 C., 760 mm. sea level and latitude 45 degrees, including a reduction of the barometer readings, brass scale, to 0 C. Log $\frac{p - \text{scale correction}}{760} \times \frac{1}{1+0.00367\ t}$ For the other corrections which may be advisable see Table 1.

logarithms with increasing weight. The least decrease that could be expected is to the figure $\bar{2}.260$ at 128 pounds. A smaller figure could not well be chosen because of the fact that in adults of the age of twenty-one years, having the extreme range of weights and normal stature (Prudential 1912 statistics), the normal calory production for males (Benedict multiple prediction formula) is not more than 3 per cent. higher than that of females. The antilogarithms of $\bar{2}.260$ and $\bar{2}.272$ differ by about this 3 per cent., and if the first were smaller the percentage difference would be larger.

Chart 4 is calculated from the Harris and Benedict[10] standard multiple prediction tables for normal basal metabolism of adults. It is impossible to put these tables in the form of logarithms. They predict the hourly calories as the sum of two numbers. They are to be used as follows. From the height in inches and the age in years read by interpolation between the family of lines a number corresponding to the lines. From the weight in pounds read on the single line the corresponding abscissa (numbers 20 to 70). The sum of these two numbers is the expected hourly calory production.

EXAMPLE.—Male, age 35, 62 inches tall, 135 pounds.

(35,62)	23
135	38
	61 predicted hourly calories.

The normal metabolism data of Benedict leaves a gap from the seventeenth to the twenty-first year. It is believed that the data of Benedict more nearly predict the normal than do those of DuBois. The data of DuBois are, however, widely used. They are included here as Chart 5 and Chart 6. Chart 5 plots the logarithms of reciprocal square meters of body surface. It is the same family of curves as that of DuBois.[11] Chart 6, due to the data of Aub and DuBois,[12] gives the logarithm of the reciprocal normal calories per square meter per hour.

Chart 3 is similar to Chart 2. It gives the logarithm of the factor reducing the observed air volume to 0 C., 760 mm. of mercury at latitude 45 degrees and sea level together with a correction to 0 C. of the mercury column and brass scale. It does not correct for aqueous vapor tension as does Chart 2 and is to be used with portable respiration apparatus. The above remarks on corrections for latitude and altitude apply equally to this chart.

Table 3 is a three place logarithm table and Table 4 is a table of antilogarithms. The logarithms of the charts consist of a mantissa, the decimal, which is always positive, and a characteristic, the integer in front of the decimal point which is negative. The signs of the characteristic are to be considered in taking the sum of the various logarithms; the characteristic of the sum is an integer which is the sum of the separate characteristics plus any digit carried to this place in adding the adjoining columns in the mantissae. The mantissa only is used in going to the table of antilogarithms and the characteristic plus one represents the number of integral digits to be pointed off in the number of the table. It fixes the position of the decimal point. In reading from Table 3 the logarithm of a number such as the hourly volume in liters assign to the mantissa of the table a characteristic one less than the integral digits in the number.

Calculation of Calory Production and Basal Metabolic Rate.—The charts are so arranged that the only calculation required is the performance of a sum.

10. Harris and Benedict: Carnegie Inst. Wash. Pub. No. 279, 1919, p. 253.
11. DuBois, D., and DuBois, E. F.: Arch. Int. Med. **17**:865 (June) 1916.
12. Aub and DuBois: Arch. Int. Med. **19**:831 (June) 1917.

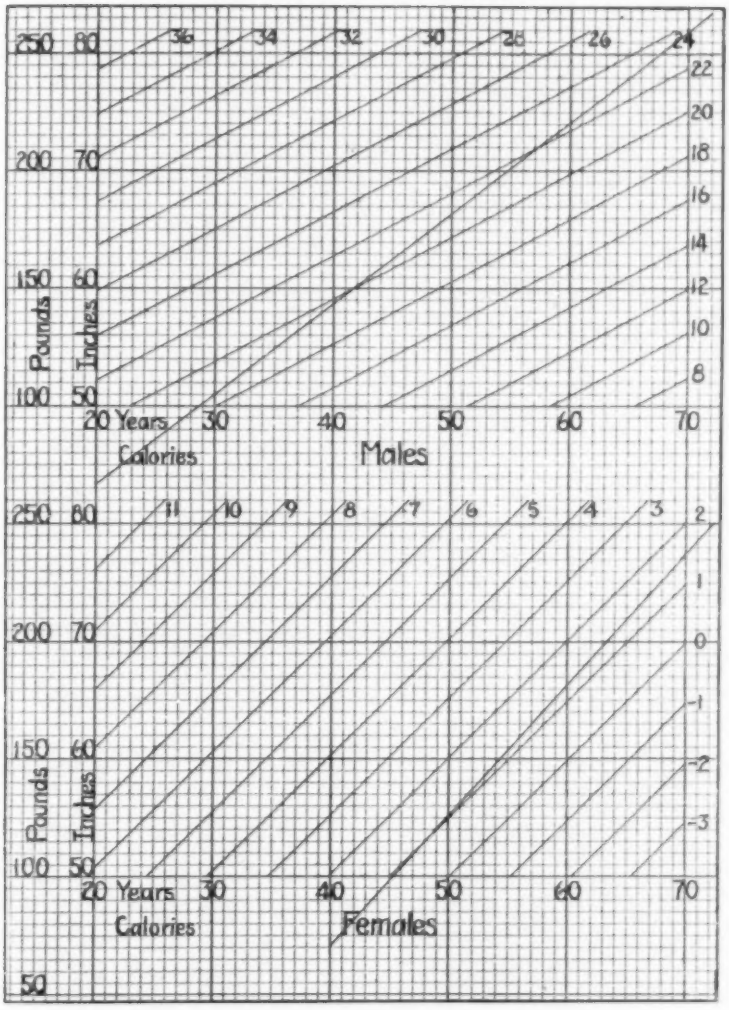

Chart 4.—The chart is based on the standard multiple prediction tables of Harris and Benedict for normal basal metabolism. From the height in inches and the age in years there is read by interpolation between the family of parallel lines a first number. The intersection of the horizontal giving weight in pounds with the single diagonal line gives an abscissa, 20 to 70. The sum of this and the first number is the normal calory production per hour. The tables of Harris and Benedict do not extend to heights below sixty inches.

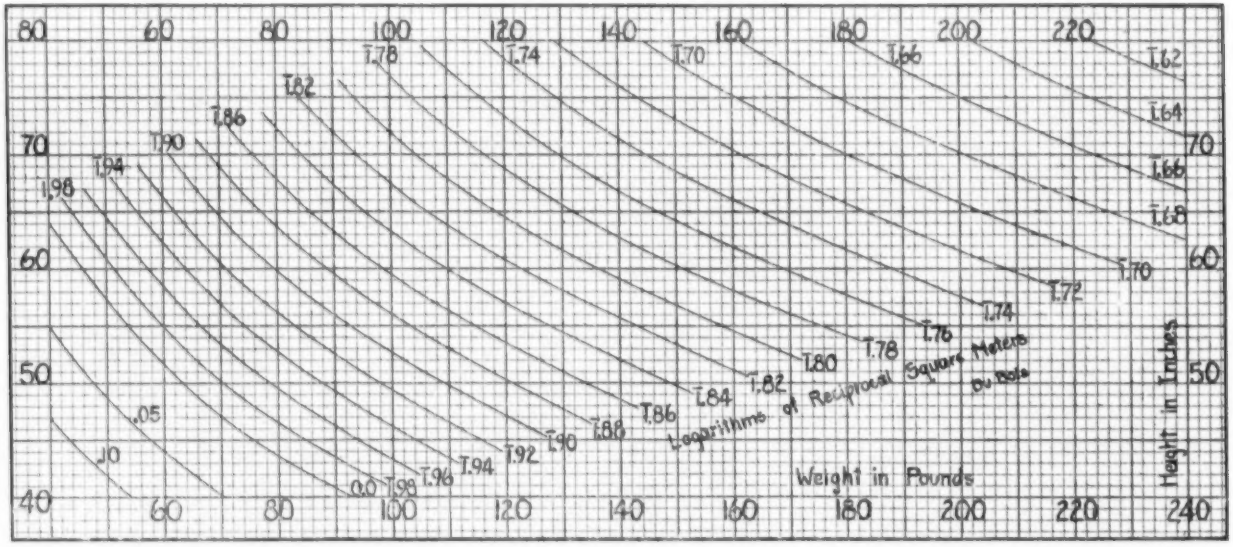

Chart 5.—The ordinates are height in inches and the abscissas weight in pounds. The curves are derived from the DuBois Height Weight formula for square meters body surface. They have been chosen so as to assign as signatures to them logarithms of the reciprocals of square meters of body surface.

To determine hourly calory production:

(a) using the Haldane apparatus.

Add the figures obtained by interpolation from Charts 1 and 2 and the logarithm, from Table 3, of the hourly volume in liters, as read on a meter or spirometer. The antilogarithm, from Table 4, of this sum is the calory production. The respiratory quotient is read directly by interpolation between the lines of Chart 1.

(b) using a direct reading oxygen consumption apparatus (Benedict, etc.).

Add to $\bar{1}.4617$ the logarithm, from Table 3, of the observed oxygen consumption per minute in c.c. and the figure obtained by interpolation from Chart 3. Before going to Chart 3 for the volume correction add to the observed temperature of the bell 1 F. as suggested by Benedict (½ C). The antilogarithm of the sum is the calory production. The respiratory quotient is assumed to be 0.82.

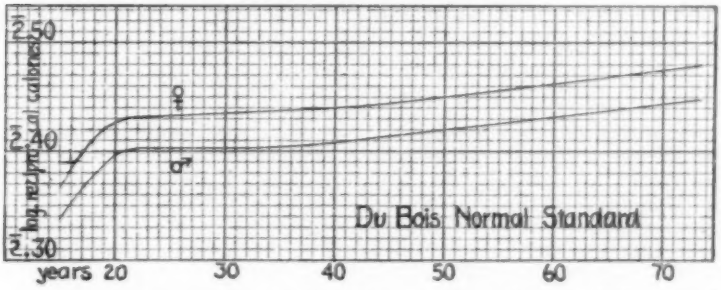

Chart 6.—The curves are the logarithms of the reciprocal of the normal hourly calory production of males and females as given by Aub and DuBois. DuBois data for males under 15 years is omitted, the data of Table 2 being preferred. In the 15 to 20 year interval DuBois data are higher than the data of Benedict. Above 20 years comparison cannot be made simply.

The hourly calory production as determined under (a) or (b) may be compared directly with the normal obtained from Chart 4. The basal metabolic rate is the quotient of the actual by the predicted. In the case of children, the basal metabolic rate determination may be made by simply adding the figure of Table 2 to the sum as obtained above under (a) or (b). The antilogarithm of this sum is then the basal metabolic rate. If it is desired to refer to the DuBois standard, add as a part of the sum the figures from Charts 5 and 6. The antilogarithm of the sum is the basal metabolic rate.

The results are given with no greater error than that inherent in the data. Each chart or table is calculated with a slightly greater degree of accuracy than the data warrant. The charts and tables are such that the basal metabolic rate is given correctly to within one unit in the second decimal place, that is

to within one per cent., and the total calory production correctly to within one-half unit in the second figure. This amount of precision necessitates the reading of Chart 1 to within two units in the third decimal place. This latter may be accomplished by applying a scale between the two CK lines in which interval the point lies and turning the scale diagonally until the ends of a ten unit interval on it fall on the two CK lines. The proportionate distance from the one line to the next of the point to be interpolated is then read off directly from the scale. The error is not over two per cent. when Chart 1 is not so taxed to its capacity. Chart 1 can easily be read more closely than the data can be calculated with a four place logarithm table and more closely than the Haldane gas buret can be read. Chart 4 can be read correctly to one-half calory, Chart 5 can be read to one-half unit in the second decimal place, and the other charts and tables are readily read to three decimals. The logarithm tables are calculated so as to be correct to one unit in the third decimal place.

EXAMPLE 1.—Haldane readings 97.32 and 79.48. Temperature 20 C.; barometer 751 mm. Hourly volume 452 liters. Male, age 38, height 65½ inches, weight 150 pounds.

Chart 1.	$\bar{1}.19$	R.Q. .83	
Chart 2.	$\bar{1}.9525$		
Log. vol.	2.655		
	1.7975	antilog. 62.7	calories per hour (actual)
		Chart 4. 24	
Chart 5.	$\bar{1}.755$	41.5	
Chart 6.	$\bar{2}.406$		
		65.5	calories per hour (expected)
	$\bar{1}.9585$	antilogarithm 0.909 B. M. R. (Du Bois)	

EXAMPLE 2.—Haldane readings 95.6 and 79.74. Temperature 18 C.; barometer 740 mm. Hourly volume 234 liters. Girl, aged 11, weight 80 pounds.

Chart 1.	$\bar{1}.405$	R.Q. .83
Chart 2.	$\bar{1}.950$	
Log. vol.	2.369	
Table 2.	$\bar{2}.305$	
	0.029	antilogarithm 1.07 7 per cent. above the normal.

EXAMPLE 3.—Average reading for contraction of Benedict spirometer bell, per minute 240 c.c. Average temperature of bell plus 0.5 F. (26 C.); barometer 746 mm. Female, aged 32, height 62 inches, weight 125 pounds.

Cal. factor	$\bar{1}.4617$		
Log. 240	2.380		
Chart 3.	$\bar{1}.9505$		
	1.7922	antilog. 62.0	calories per hour (actual)
		Chart 4. 6	
Chart 5.	$\bar{1}.805$	50	
Chart 6.	$\bar{2}.435$		
		56	calories per hour (expected)
	0.0322	antilogarithm 1.08 B.M.R. (DuBois)	

SUMMARY

Tables and charts have been prepared by means of which the basal metabolic rate may be calculated by simply adding five numbers.

The charts condense the usual tables into a very small space. They include one reducing saturated gas volumes to 0 C. dry, 760 mm. mercury, sea level, 45 degrees latitude with a temperature pressure correction for the brass or glass scale of the barometer.

THE NATURE OF THE SO-CALLED "CAPILLARY PULSE"

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The "capillary pulse" has been of interest to clinicians ever since Quincke [1] first called attention to it in 1868. Nothing, however, has been added to his original description of the condition, nor to his discussion of the probable mechanism by which it is brought about. Two observers before Quincke noted the phenomenon in isolated cases, but failed to appreciate the frequency of its occurrence or its significance. Lebert [2] cites the case of a patient with an aortic aneurysm who exhibited systolic flushing and diastolic paling of the cheeks. Ascherson [3] observed a child 7 years of age with varicella following scarlatina, in whom the papules and the bases of the vesicles reddened in diastole and paled in systole. This was very evident for four days, but after that it was only demonstrable when the skin about the lesion was stretched. Both authors attributed the phenomenon to a pulsation of the capillaries. It was Quincke, however, who observed the flushing and paling of the tissues under the finger nail not only in aortic insufficiency, but in a variety of other conditions. In patients with incompetent aortic valves it is most manifest, but it can be observed in many normal individuals. Quincke calls to mind that ordinarily, because of the elasticity of the arteries, the blood flows through the capillaries in a continuous stream; but that with venous obstruction, or with a marked lowering of the blood pressure associated with a slow pulse rate, the capillary flow may become pulsatile. A marked relaxation of the arterial wall may have the same effect. Thus Claude Bernard explained the pulsation of the capillaries and veins of the submaxillary gland which he observed on stimulation of the chorda tympani. In a later paper Quincke [4] emphasizes that a great difference between the systolic and diastolic pressures is essential for the visualization of the capillary pulse. He observed the phenomenon in anemic individuals, and in those with low blood pressure, an overactive heart, and a pulse

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1. Quincke, H.: Beobachtungen ueber Capillar und Venenpuls, Berl. klin. Wchnschr. **5**:357, 1868.

2. Lebert: Handb. der praktischen Medicin, Ed. 3, **1**:746, 1863.

3. Ascherson: Variola Versicolor, Medizin. Ztg. d. Ver. f. Heilk. in Preussen, 1834.

4. Quincke, H.: Ueber Capillarpuls und Centripetalen Venenpuls, Berl. klin. Wchnschr. **27**:263, 1890.

of the collapsing type, as well as in those with a leaking aortic valve. In his first paper Quincke described the pulsation under the finger nail, both with and without the application of gentle pressure. Subsequently, however, he noted it on the mucous membrane of the lip, when compressed with a glass slide, and on the skin of the forehead after it had been rubbed with a blunt object. When a patient exhibiting this phenomenon presents a skin lesion, such as erisypelas or urticaria, the pulsation becomes very evident.

Quincke's observations and conclusions have been generally confirmed and accepted, and we find in most textbooks of medicine, as well as of physiology, a presentation of the views first set forth by him fifty-three years ago. Lombard [5] in 1912 described a method by which the human capillaries can be studied directly under the microscope, but in the United States little use has been made of his observations, save by Danzer and Hooker,[6] who devised a method of measuring the capillary pressure, based on this principle. If a drop of glycerin or castor oil be applied to the skin at the base of the finger nail, and this area be then studied through the microscope under direct illumination, with a magnification of from 40 to 80 diameters, the capillary loops are beautifully visualized. Not only can the architecture of the capillary bed be studied, but the blood flow can be observed almost as well as in the classical demonstration of the capillary circulation in the web of the frog's foot. For details of technic, Danzer and Hooker's article, as well as of Weiss' [7] studies should be consulted.

While engaged in a study of the capillary morphology and blood pressure in a series of many different types of cases, I had the opportunity to observe the capillaries in eleven patients who exhibited a well marked clinical capillary pulsation under the finger nail. The capillaries in these cases were studied most assiduously under all kinds of conditions, and in no instance was a pulsatory stream of the blood in the capillaries seen.

Method.—A description of the method employed will be in place A drop of clear castor oil is placed on the dorsum of a finger just below the nail bed, and the finger is then placed on the finger rest of Danzer and Hooker's microcapillary tonometer, which stands on the stage of the microscope at heart level. Light is thrown on the area

5. Lombard, W. P.: The Blood Pressure in the Arterioles, Capillaries and Small Veins of the Human Skin, Am. J. Physiol. **29**:335, 1912.

6. Danzer, C. S., and Hooker, D. R.: Determination of the Capillary Blood Pressure in Man with the Micro-capillary Tonometer, Am. J. Physiol. **52**: 136, 1920.

7. Weiss, E., and Dieter, W.: Die Strömung in den Kapillaren und ihre Beziehung zur Gefässfunktion, Zentralbl. f. Herz. u. Gefässkrankh. **12**:295, 1920.

to be observed by an electric bulb whose rays are focused by a condenser. A magnification of eighty diameters is employed. The capillaries are thus clearly brought into view and can be studied at leisure. Patients with a clinical capillary pulse are, however, difficult to study, because the finger moves with each pulse beat and the capillaries are thus thrown out of focus. This results in a very deceptive microscopic picture, for the finger movements rhythmically alter the focus of the microscopic field under observation. Thus with each pulse beat the capillaries become indistinct and may even disappear from view, to reappear immediately thereafter with their original clearness. This movement in and out of the focal field can readily be mistaken for a pulsation of the capillaries themselves. However, a close study, which, to be sure, is somewhat trying on the eyes, will convince the observer that the blood stream through the capillaries is at all times continuous and never pulsatile.

When the capillary blood stream is studied in this manner, it will be found that in most instances the flow is so rapid and steady that it can hardly be visualized. Each capillary is of a constant and uniform caliber. However, in individual capillaries the flow may be slow and almost halted at times but soon resumes its rapid streaming. Some individuals have a slower flow than others, and some a more rapid flow. With hypertension the velocity of the capillary blood appears to be increased; in arteriosclerosis it is decreased. But in spite of these individual variations, a capillary pulse was never observed. There was no intermittency of the circulation in the capillaries, nor was there any systolic lateral displacement of the capillaries.

Because of the fact that clinically the "capillary pulse" is usually observed best under slight pressure of the tissues, such pressure was exerted on the area studied by means of the Danzer-Hooker instrument. The pressure was elevated until the flow through the capillaries ceased, and was then gradually released to zero. At no pressure, not even with the first reappearance of the flow, was there the slightest departure from the normal continuous stream of blood. Both Weiss [7] and Jürgensen [8] have described pulsation of the capillaries observed through the microscope, but I am compelled to disagree with their findings. It is probable that the pulsation of the finger, discussed above, led them astray. I have seen this simulated capillary pulsation when the capillary flow was at a standstill because of the high pressure in the air chamber of the tonometer. Such an observation allows of no two interpretations and shows clearly with what care the studies must be made to avoid error.

The accompanying table gives a brief summary of the cases studied, together with the capillary pressure found in each instance. For reasons which will be detailed in a subsequent article, I have not averaged the pressures read in the different capillaries as advocated by Danzer and Hooker, but prefer to record them as individual readings. It seems quite certain that the variations of pressure observed in the same individual are of significance, and are not due to inaccuracy of measurement.

PATIENTS EXHIBITING CLINICAL CAPILLARY PULSE BUT NO MICROSCOPIC PULSATORY CAPILLARY FLOW

Case	Age	Sex	Diagnosis	Blood Pressure	Capillary Pressure, Mm. Hg	Room Temp., F.	Appearance of Capillaries
1	21	Male	Aortic insufficiency, rheumatic	140/ 50	10 10	..	Arrangement regular, some looped; subpapillary plexus visible
2	23	Male	Aortic insufficiency, rheumatic	115/ 60	20 20 18 25 22 23 26 15	78	Capillaries long, few loops
3	28	Male	Aortic insufficiency, rheumatic	140/ 50	20 18.5 10 13.5 17 10 11 8	66	Capillaries numerous, many rows, few tortuous; subpapillary plexus visible
4	18	Female	Aortic insufficiency, rheumatic	190/ 0	17 17.5 17	67.5	Capillaries numerous, not tortuous; subpapillary plexus visible
5	20	Male	Aortic insufficiency, mitral stenosis, rheumatic	150/ 20	8 5 7 12 12 7 10 16.5 15	70	Capillaries very long and numerous
6	12	Male	Aortic insufficiency, rheumatic	110/ 40	10 16 9 10.5	70	Capillaries very convoluted and irregular
7	8	Male	Aortic insufficiency, mitral stenosis, rheumatic	100/ 40	5 4 5 3	70	Capillaries normal
8	76	Male	Hypertension right hemiplegia	180/ 60	25 24 21 25 27 21 20	68	Capillaries long, convoluted; extensive subpapillary plexus
9	55	Male	Hypertension	205/110	17 31.5 12 19.5 23 22.5 18 18 17 26.5 34 38 29 28	65	Capillaries long, many convoluted; some giant capillaries
10	57	Female	Hypertension	145/ 75	25 20 27 23 18 14 30 21	75	Capillaries very convoluted; several rows; flow rapid
11	63	Female	Hypertension, diabetes	210/ 85	26 13 27 15 22 21 35 23 10 11.5 17 14.5	88	Longer and more tortuous than normal; subpapillary plexus prominent

Since, according to these observations the current views on the nature of the "capillary pulse" are erroneous, we must seek a new explanation of the phenomenon. At first thought it would seem that if the capillaries are not concerned in the production of this pulsation, it must be the minute arterioles in the subpapillary plexus of the skin which bring it about. This may be so in many instances, but Quincke's observations on the centripetal venous pulse, published in the same articles as those on the capillary pulse, suggest another possible interpretation. In some patients who exhibited clinical capillary pulsation he noted a post systolic centripetal pulsation of the veins on the dorsum of the hand. He believed it to be due to the propagation of the arterial pulse wave through the capillaries to the veins. In his second paper, however, he states that the capillary pulse is uncommonly found associated with the venous pulse. It is not quite clear how this comes about. Jürgensen [8] offers a possible explanation. He reviews the work of Hoyer,[9] Grosser [10] and Schumacher,[11] who demonstrated direct anastomoses between the arterioles and venules in the subpapillary plexuses, to explain some of the phenomena which he has observed in his studies of the capillaries. It is possible that the venous pulse, when it occurs, is caused by the transmission of the pulse wave through these subpapillary anastomoses, and that the clinical capillary pulse may be due to a pulsation of the subpapillary venules as well as arterioles. Additional evidence that the capillaries are not necessarily associated with the color of the skin is found in Weiss' [12] observation that on the skin of the cheek the capillaries are relatively scanty while the subpapillary venous plexuses are especially well developed, thus playing a dominant part in the production of the color of the skin of the cheek.

CONCLUSIONS

The so-called "capillary pulse" is not a manifestation of a pulsation of the capillaries, but is due to an exaggerated pulsation of the arterioles and possibly of the venules of the subpapillary plexus of the skin. In view of this fact it would be well to discard the term "capillary pulsation" and to speak of the systolic flushing of the skin.

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8. Jürgensen, E.: Microkapillarbeobachtungen, Deutsch. Arch. f. klin. Med. **132**:204, 1920.

9. Hoyer, H.: Ueber unmittelbare Einmündung kleinster Arterien in Gefässe venösen Charakters, Arch f. mikroskop. Anat. **13**:603, 1877.

10. Grosser, O.: Ueber arteriovenöse Anastomosen an den Extremitätenden beim Menschen und den krallentragenden Säugethieren, Arch f. mikroskop. Anat. **60**:191, 1902.

11. v. Schumacher, S.: Ueber das glomus coccygeum des Menschen, etc., Arch. f. mikroskop. Anat. **71**:58, 1908.

12. Weiss, E., and Holland, M.: Zur Morphologie und Topographie der Hautkapillaren, Ztschr. f. exper. Path. u. Therap. **22**:108, 1921.

THE ETIOLOGY AND DEVELOPMENT OF GLOMERULONEPHRITIS *

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There are four well established types of renal disease that must be considered in a discussion of nephritis. A brief explanation of each of these will be given in order to establish the limitations of the group under discussion.

1. *Pyelonephritis.*—This is an acute or chronic exudative inflammation distributed in patches throughout the kidneys, and extending from the cortex throughout the pyramids into the pelvis. It is caused by bacteria, usually staphylococci or colon bacilli. In most instances the bacteria are carried to the kidney by the blood; but in cases of obstruction of the lower urinary tract they may enter from the urine. In the earlier stages of a hematogenous infection, before there has been extension to the pelvis, the lesions are spoken of as abscesses. Extension of the infection to the capsule may produce perinephritis or perirenal abscess. Infection of a dilated pelvis causes pyonephrosis. The disease is frequently unilateral and acute cases are sometimes mistaken for appendicitis or other acute abdominal conditions. Cases vary in intensity from mild to severe. The treatment of severe unilateral cases is usually surgical. Bilateral pyelonephritis may result in renal insufficiency but there is seldom any confusion clinically with Bright's disease.

Acute interstitial nephritis is related to this group in that it is an exudative inflammation of the interstitial tissues. The kidneys show areas of cortex infiltrated with lymphocytes of intermediate size and plasma cells. Apparently there is never enough of the kidney involved to produce renal insufficiency. There is evidence in one of our cases (Case 51) that the exudate remains in the kidney indefinitely and gives rise to areas of cortical atrophy; but no chronic nephritis of this type is known. Acute interstitial nephritis occurs frequently during scarlet fever, and rarely in other infections, such as diphtheria and congenital syphilis. It is seldom of much importance clinically, being overshadowed by the associated disease.

The spontaneous chronic nephritis of laboratory animals is more closely related to pyelonephritis than to any other form of human renal

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* Aided by grant from the National Dental Association.

disease. It is characterized by lymphocytic exudates in the renal parenchyma, which ultimately cause cortical atrophy to such an extent that the kidneys are shrunken and their surfaces covered with small depressions. The pelvis is not extensively involved, as a rule. Death from renal insufficiency is rare, and the majority of cases result in healing. This is the form of nephritis usually obtained in animals by experimental procedures. There is a gross resemblance between the kidneys of chronic Bright's disease and those of this animal infection; but clinically, histologically and in manner of development there is no similarity.[1] There is no known animal disease corresponding to chronic Bright's disease.

2. *Nephrosis.*—This term is applied to renal lesions of a purely degenerative character in contrast to *nephritis* in which the phenomena of reaction (exudation, proliferation) have appeared. This group is not sharply separable from glomerulonephritis since cases of degeneration occur in which it is very difficult to determine whether there are any reactive changes in the glomeruli. Again, there are degenerative changes of greater or less degree in practically all cases of glomerulonephritis, and in a large percentage of arteriosclerotic kidneys. It is, however, very desirable to limit the term nephrosis to degenerative lesions in which there is no pronounced involvement of the glomeruli or blood vessels.

Nephrosis is by far the commonest form of renal disease seen at necropsy and it is the most frequent cause of albuminuria. It is found at necropsy in practically all severe infectious diseases and infections, in obscure toxemias such as the toxemia of pregnancy, in chemical poisoning (mercury, arsenic, phosphorus, and many other substances), in severe jaundice, and in severe cardiac decompensation. It is presumably present in life in the above named conditions when albumin or casts are found in the urine. When found at necropsy it is proof of some form of toxemia.

The amyloid kidney, although usually classified as a nephrosis, is better understood as a special form of glomerulonephritis.

Clinically, nephrosis is usually definitely secondary to some associated disease, and the differentiation from Bright's disease under these circumstances presents no difficulties; but in cases of obscure etiology the distinction is not made so readily. There are no cases in our series of chronic nephrosis such as is described by Volhard and Fahr [2] as "genuine" nephrosis. It seems that a case of primary chronic renal disease should rarely, if ever, be regarded as a nephrosis.

1. Bell and Hartzell: Spontaneous Nephritis in the Rabbit, J. Infect. Dis. **24**: 628, 1919.

2. Volhard and Fahr: Die Brightsche Nierenkrankheit, Berlin, 1914.

The clinical findings attributable to the kidney in nephrosis are usually mild; but renal insufficiency may develop in severe cases. There is never hypertension or cardiac hypertrophy. Severe nephroses are usually rapidly fatal.

In mild nephroses at necropsy the kidneys show cloudy swelling. In severe cases there is cloudy swelling, fatty degeneration and sometimes necrosis of tubules and glomeruli.

3. *Arteriosclerosis of the Kidneys.*—Two forms of this disease may be distinguished on clinical and anatomic grounds.

(*a*) THE SENILE TYPE (Arteriosclerotic atrophy): In advanced age and especially in association with generalized senile arteriosclerosis, one often finds small kidneys with adherent capsules and rough granular or pitted surfaces. This appearance is due to an irregular atrophy of the more superficial parts of the cortex which is caused by narrowing of some of the arteries. Usually the larger branches are the ones chiefly affected and the disease is never restricted to the arterioles. The senile kidney is seldom of any clinical importance since the amount of cortex destroyed is relatively small; but in occasional instances the atrophy is so extensive that renal insufficiency develops. It has not been determined how often arteriosclerotic atrophy gives rise to the clinical picture of chronic Bright's disease.

(*b*) THE HYPERTENSION TYPE: In many cases of chronic hypertension normal kidneys are found at necropsy and in some a glomerulonephritis is found; but a large percentage of cases are associated with disease of the renal arteries. When no disturbance of renal function is demonstrable we speak of essential hypertension, but when there is evidence of serious renal injury we consider the condition chronic Bright's disease. The kidneys from cases of essential hypertension usually show hyaline degeneration of some of the afferent glomerular arteries and often there is also disease of medium sized and small arteries, and there are gradual transitions between the slight involvement of the arteries in these cases and the extensive involvement in chronic Bright's disease of the vascular type. The majority of patients with essential hypertension die of cardiac or cerebral complications without developing serious renal involvement, but some cases extensive destruction of renal tissue occurs and they are then regarded as being cases of chronic Bright's disease of the arteriosclerotic type. There are about twenty-six examples of this form of Bright's disease in our series of 3,300 necropsies. We expect to discuss this subject fully in a subsequent report.

4. *Glomerulonephritis.*—This group includes renal disease in which the structural changes are due almost entirely to primary inflammatory and degenerative changes in the glomeruli. It includes all acute and subacute and a majority of chronic cases of Bright's disease.

The older terms "chronic parenchymatous" and "chronic interstitial" correspond to stages or degrees of severity of glomerulonephritis. They do not designate any important feature of the disease and a large number of cases are intermediate in type, i. e., neither typical parenchymatous nor typical interstitial. This terminology has another element of confusion in that some observers consider the arteriosclerotic kidney as chronic interstitial nephritis. The literature of nephritis would be clearer if these older terms were discarded.

Chronic glomerulonephritis is not sharply separable from the arteriosclerotic kidney since a few cases of the former show some disease of the renal arteries; but these borderline cases are not very numerous and we see no justification for the view that the two diseases are indistinguishable (Moschcowitz [3]). Certainly the great majority of cases are anatomically distinct, although they may be indistinguishable clinically. It may be, as Ophüls [4] believes, that the same toxin attacks the arteries in one case and the glomeruli in another and that the differences are really only anatomic; but it seems better to adhere to anatomic distinctions until we know more about the etiology of arteriosclerosis.

MATERIAL

Microscopic sections from the kidneys of about 3,300 consecutive necropsies have been examined. Small pieces of kidney from nearly all of these had been preserved so that it was possible to make serial sections when desirable. The clinical history and gross necropsy findings were always considered, but the final diagnosis was usually made on the microscopic appearances. All the subacute and chronic cases had been recognized clinically or at necropsy, but many of the acute cases had been overlooked. Sixty-nine cases of glomerulonephritis were identified. In a number of the acute cases nephritis was not the main cause of death, and these kidneys furnish abundant illustrations of the early stages of the disease.

We have arranged our cases somewhat arbitrarily into acute, subacute and chronic groups. There are striking clinical and pathologic differences between typical examples of each group, but there are many intermediate forms and one may easily become convinced from the study of a large series that there is a fundamental relationship between the different forms of glomerulonephritis. Senator [5] called attention to this point many years ago. As will be brought out later, one of the

3. Moschcowitz, E.: Clinical and Anatomic Relations in Chronic Nephritis, Arch. Int. Med. **26**:259 (Aug.) 1920.

4. Ophüls, Wm.: Arteriosclerosis and Cardiovascular Disease, Stanford Univ. Pub., Med. Sc., **1**:1, 1921.

5. Senator, H.: Nothnagel's Encyclopedia of Practical Medicine, 1905, Am. Ed., p. 180.

arguments for the infectious origin of chronic glomerulonephritis is that it is linked to the acute form by numerous intermediary cases.

ACUTE GLOMERULONEPHRITIS

There are thirty-two acute cases. Brief protocols of each will be given. Cases 1 to 9 are mild cases in early stages in which death was due to extrarenal causes. In Cases 1 and 2 only a minority of the glomeruli are involved.

Case 1 (A-16-182).—Female, aged 35 years. Case of advanced chronic aortic and mitral endocarditis with fresh thrombi on the thickened leaflets. Kidneys weighed 260 gm.; no gross changes. Some of the glomeruli showed changes in a few of their lobules. These changes consisted in swelling of the endothelium, partial closure of capillaries, and accumulation of polymorphonuclears in the capillaries. The majority of the glomeruli are entirely normal. This represents an early glomerulitis of very limited extent.

Case 2 (A-19-276).—Male, aged 16 years. Acute endocarditis. During the last week of life, blood culture on two occasions gave hemolytic streptococci. Hematuria. Leukocytes, from 20,000 to 42,000. Necropsy: Heart weighed 620 gm.; many large thrombi on mitral and aortic leaflets. Infarcts in kidneys and spleen. Kidneys not enlarged. Many petechial hemorrhages. Some glomeruli showed swelling of endothelium with partial closure of capillaries. Majority were normal.

Case 3 (A-19-58).—Male, aged 39 years. Chronic mitral endocarditis with fresh thrombi on the stiffened leaflets. Leukocytes, 11,200. Heart weighed 585 gm. Kidneys not enlarged; all glomeruli much enlarged. There are a number of polymorphonuclears in the capillaries. The endothelial swelling is not sufficient to close any of the capillaries. There is moderate injury of the tubules but no atrophy.

Case 4 (A-20-94).—Male, aged 61 years. Had a suppurative infection of the right carpus for two months before death. Erysipelas of face and neck the last five days of life. No examination of urine. Necropsy: Suppuration of carpus with partial destruction of the os magnum. Erosion of the cartilaginous surfaces. Spleen weighed 550 gm. Hemolytic streptococcus in pure culture from the spleen. Large numbers of gram-positive cocci demonstrable in sections of the spleen. Kidneys weighed 370 gm. Cloudy cortices. Glomeruli are not enlarged, but their capillaries contain many polymorphonuclear leukocytes.

Case 5 (A-20-118).—Female, aged 15 years. Normal labor February 11. Fever began four days later. Continuous fever and leukocytosis. Streptococcus from blood culture, February 28. Death, March 13, 1920. Necropsy: 1,500 c.c. pus in right pleural cavity. Large thrombus on tricuspid valve. Abscess of right lung. Spleen weighed 260 gm. Kidneys weighed 295 gm. Cloudy cortices. Glomeruli not enlarged. No swelling of endothelium. A number of polymorphonuclears in some of the glomerular capillaries.

Case 6 (A-20-220).—Male, aged 55 years. Death from chronic myocardial degeneration and chronic alcoholism; no clinical history; no edema. A small amount of fluid found in the pleural cavities. Heart weighed 520 gm.; spleen, 335 gm.; kidneys, 397 gm. Glomeruli are all enlarged. There is moderate swelling of the endothelial cells, with partial closure of some capillaries. Many polymorphonuclears in the capillaries.

Case 7 (A-21-144).—Male, aged 20 years. Measles in November, 1919, complicated by bilateral suppurative otitis media. Discharge from the ears for several weeks. Present illness began about four weeks before death with septic sore throat, complicated by acute bilateral suppurative otitis media. Both

tympani were incised. Discharge from ears continued until March 20. Symptoms of meningitis appeared March 20. Lumbar puncture, March 21, gave a purulent fluid. The urine showed a faint trace of albumin at times. Death March 22. Necropsy: purulent meningitis; streptococci in smears. Bilateral suppurative otitis media with mastoiditis. Kidneys were not enlarged but showed cloudy cortices. Glomeruli not enlarged. There is no notable swelling of the endothelium but the capillaries contain large numbers of polymorphonuclears.

Case 8 (A-17-114).—Female, aged 44 years. Death from lobar pneumonia. No edema. No urinalysis. May 19, 10,900 leukocytes. Blood pressure 115/88. Death May 23. Necropsy: lobar pneumonia. Heart weighed 310 gm.; kidneys, 310 gm. Pale cloudy cortices. All glomeruli slightly enlarged. Large numbers of polymorhponuclears in the capillaries. No swelling of the endothelium.

Case 9 (A-13-24).—Male, aged 55 years. Had nosebleed at frequent intervals for two weeks before death. No edema. Urine not examined. Necropsy: pneumococcus bacteremia; acute bronchopneumonia (small areas); localized suppuration in the pharynx which extended deep into the pharyngeal tissues. Kidneys weighed 400 gm. and contained a large number of small peripheral infarcts which were due to thromboses of the small arteries. Most of the glomeruli are enlarged and the capillaries are partly occluded by the swollen endothelial cells. An occasional polymorphonuclear leukocyte is seen in the glomerular capillaries.

Cases 10 to 21 are examples of fairly severe glomerulonephritis in which the renal condition was obscured by the associated disease.

Case 10 (A-13-190).—Female, aged 35 years. History of many sore throats. Inflammatory rheumatism at 15. Has deformities of joints and swelling of feet. November 7, blood pressure 126/110. Urine: faint trace of albumin, November 6 and November 28. Leukocytes, December 6, 5,500; December 26, 26,600; 95 per cent. polymorphonuclears. Streptococcus from blood culture. Clinical diagnosis: cardiac hypertrophy, endocarditis, mitral insufficiency, terminal bacteremia. Death, December 27. Necropsy: edema of ankles. Heart weighed 525 gm.; mitral stenosis; fresh thrombi on mitral valve and mural thrombosis of left ventricle. Kidneys not enlarged, but cloudy. Glomeruli are all greatly enlarged. A large percentage of the capillaries are partly or completely occluded by the swollen endothelium. Many capillaries contain numerous polymorphonuclear leukocytes.

Case 11 (A-14-49).—Male, aged 25 years. Has had arthritis at intervals for many years. Present illness began about Dec. 1, 1913, with dyspnea and swelling of the legs and face. Admitted to Hospital, Feb. 13, 1914. Marked dyspnea. Temperature, 102 F. on admission; later not over 100 F. Urine: traces of albumin during February, severe albuminuria in March. Feb. 14, 13,600 leukocytes. Clinical diagnosis: cardiac hypertrophy and endocarditis. Death, April 4, 1914. Necropsy: general anasarca, ascites, hydrothorax. Heart weighed 575 gm.; chronic mitral endocarditis; many large thrombi on aortic leaflets. Spleen, greatly enlarged. Kidneys enlarged and cloudy. Glomeruli are all enlarged and show partial closure of the capillary lumina, due to swelling of the endothelium. There are very few polymorphonuclears in the glomeruli. No tubular atrophy.

Case 12 (A-14-255).—Male, aged 39 years. Patient was taken ill with a cough and fever after working three days in a wet trench. Diagnosis of pneumonia, made by a physician four days later (Nov. 23, 1914). Admitted to hospital, December 1. Leukocytes, 20,000. Urine: moderate albuminuria, numerous hyalin and granular casts. No edema. Clinical diagnosis: lobar pneumonia. Death, December 12. Necropsy: Lobar pneumonia; large thrombi on aortic leaflets. Kidneys weighed 405 gm. The glomeruli are greatly enlarged

and the capillary lumina are partially occluded by swollen endothelial cells. There are many polymorphonuclear and some large mononuclear cells in the capillaries. No atrophy of the tubules.

Case 13 (A-13-165).—Male, aged 33 years. Had acute articular rheumatism a few years ago. Four months ago he first noticed shortness of breath and swelling of feet. Symptoms became more intense. Purpuric rash appeared on lower extremities on October 1. Admitted to hospital, October 4. Leukocytes, 15,800. Urine: albumin, numerous hyalin and granular casts. Death, October 21. Necropsy: moderate anasarca, ascites. Heart weighed 640 gm.; chronic mitral endocarditis with many fresh thrombi on mitral and aortic leaflets. Spleen weighed 595 gm.; kidneys, 460 gm. Glomeruli moderately enlarged. Partial closure of capillaries. A number of polymorphonuclears in the capillaries. No tubular atrophy.

Case 14 (A-15-97).—Female, aged 29 years. Illness of nine weeks' duration. Continuous high fever. Pus in urine. No edema. Leukocytes, 13,500. Necropsy: acute vegetative mitral and aortic endocarditis. Infarction of spleen. Kidneys cloudy but not enlarged. Glomeruli are all moderately enlarged. The capillaries are partially closed and contain large numbers of polymorphonuclears.

Case 15 (A-15-230).—Male, aged 34 years. Acute symptoms began about April 1, 1915. Cough, night sweats, pulmonary hemorrhage. Temperature 97 to 102. Tubercle bacilli in sputum. No edema. Death, July 16, 1915. Necropsy: ascites (700 c.c.). Pulmonary tuberculosis with cavities. Intestinal ulcers. Heart weighed 320 gm.; kidneys, 490 gm. Glomeruli all moderately enlarged. Increased number of nuclei. Partial closure of many capillaries by swollen endothelium; complete closure of some. A number of polymorphonuclears in some glomeruli. No tubular atrophy (Fig. 1).

Case 16 (A-15-323).—Male, aged 49 years. First hospital admission in June, 1914. Discharged. Readmitted, Aug. 3, 1915. Recurrent attacks of arthritis. Loss of weight and strength. Dyspnea. Edema. Enlarged heart. Dilated aortic arch. Right pleural cavity aspirated several times. Blood Wassermann, positive. Urine, August 5: albumin and casts. Blood pressure, August 11, 160/110. Death, Oct. 18, 1915. Necropsy: ascites (200 c.c.) hydrothorax. Enlarged heart; advanced mitral stenosis with ulceration; aneurysm of arch of aorta. Kidneys weighed 320 gm. A number of glomeruli appear as abscesses because of the enormous number of polymorphonuclears present (Fig. 2); in other glomeruli there are only a few polymorphonuclears. A fairly large proportion of the glomeruli show epithelial crescents (the extracapillary type of glomerulitis). There is no appreciable swelling of the endothelium. This case represents a blending of the pyelonephritis group with the extracapillary form of glomerulonephritis. There are large numbers of polymorphonuclears in the tubules. No tubular atrophy.

Case 17 (A-16-48).—Male, aged 58 years. Diabetic gangrene of foot. No edema. Blood pressure, February 8, 140/110. Urine, February 9: trace of albumin and a small amount of pus. February 5, 13,500 leukocytes; 91 per cent. polymorphonuclears. Death, February 10. Necropsy: ascites (200 c.c.); right hydrothorax (400 c.c.). Heart weighed 370 gm. *Streptococcus pyrogenes* secured from heart's blood. Kidneys weighed 573 gm. Cloudy cortices. Large numbers of polymorphonuclears in the glomeruli, tubules and interstitial tissue (Fig. 3). Glomeruli are all enlarged. Marked increase of nuclei and partial closure of capillaries by swollen endothelium. No tubular atrophy.

Case 18 (A-16-165).—Male, aged 35 years. Became intoxicated and was injured in an automobile accident April 20. Superficial injuries. No broken bones. Admitted to hospital, April 22. Temperature around 101 F. Excessive hematuria, vomiting, hiccoughing. Leukocytes, 15,000; 82 per cent. polymorphonuclears. No edema. Death, April 26. Necropsy: heart weighed 345 gm.; kidneys, 415 gm.; cloudy cortices. No focus of infection found. Blood

culture sterile. Glomeruli are all moderately enlarged and show great increase of nuclei. Capillaries are partially closed by swollen endothelium. Many polymorphonuclears in the capillaries. No atrophy of tubules.

Case 19 (A-17-202).—Male, aged 25 years. Acute arthritis in 1908 and again in 1909. Smallpox in 1910. History of cardiac disease for the past six years. Frequent appearance of petechial hemorrhages in the skin since February, 1917. These would disappear, then reappear after a variable interval. Admitted to hospital Aug. 20, 1917. On admission there was marked cardiac hypertrophy, enlargement of spleen and edema. Urine: abundant albumin, casts found at one examination. Leukocytes, August 21, 4,700; 70 per cent. polymorphonuclears. Septic temperature. Phenolsulphonephthalein, August 23, 65 per cent.; September 14, 45 per cent. One blood culture sterile. Blood pressure, October 3, 140/80. Death, Oct. 4, 1917. Necropsy: anasarca, ascites, hydrothorax. Adherent pericardium. Heart weighed 600 gm.; old ulcerative

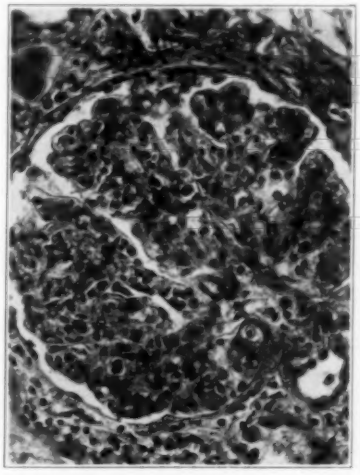

Fig. 1.—Case 15. Proliferative glomerulitis, intracapillary type. Low magnification.

mitral lesion with many large fresh thrombi. Spleen weighed 1400 gm.; kidneys, 515 gm. All glomeruli are greatly enlarged with a notable increase of nuclei. The capillaries are largely closed by the swollen endothelium. There are only a few polymorphonuclears in the glomeruli. Some of the tubules show an early stage of atrophy. There are no embolic lesions in the glomeruli although one would expect this lesion with the type of involvement of the heart and spleen.

Case 20 (A-18-9).—Female, aged 3 months. Marked jaundice developed October 2. Admitted to hospital, Oct. 4, 1917. Marked jaundice and exophthalmos. Enlargement of liver and spleen. Emaciation. No edema. Wassermann positive. Hemoglobin, 35 per cent. Erythrocytes, 2,500,000. Bile and pus in the urine. Treated for congenital syphilis. Attack of lobar pneumonia, Jan. 3, 1918. Partial recovery from the pneumonia, but fever and listlessness persisted. Leukocytes, Jan. 16, 1918, 14,800. Death, January 17. Necropsy: 100 c.c. of thick pus in peritoneal cavity, and fibrinopurulent exudate over

both lungs. Kidneys weighed 45 gm.; pale, cloudy cortices mottled with hemorrhages. Pneumococci in smears from pus from serous cavities and in pure culture from the blood. A large percentage of the glomeruli show infarction due to thrombosis of the afferent arteriole (Fig. 4). The majority of the glomeruli show no special abnormality. There is no swelling of the endothelium, and there are very few polymorphonuclears in the capillaries. There is severe tubular degeneration.

CASE 21 (A-18-122).—Male, aged 30 years. Dated his present trouble from March 1, 1918. Abundant albumin in urine. No other clinical data. Death, June 11, 1918. Necropsy: general anasarca, hydrothorax, hydropericardium. Heart weighed 565 gm. Numerous large vegetations on mitral and aortic valves. Spleen weighed 680 gm.; contained several infarcts. Kidneys weighed 530 gm. Cortices thickened, clouded and yellowish. Chronic passive congestion of viscera. The glomeruli are nearly all moderately enlarged and

Fig. 2.—Case 16. Glomerular abscess.

show an increased number of nuclei. There is swelling of the endothelium and narrowing of the capillaries, but only a small per cent. of the capillaries are completely closed. There are many mononuclear leukocytes in the capillary lumina. Some of these may be endothelial cells that have separated off from the walls. There is moderate injury of the tubules but no atrophy.

Cases 22 to 32 may be considered fairly typical clinical examples of acute glomerulonephritis.

22. (A-13-140).—Female, aged 12 years. After a severe cold, about June 7, 1913, patient developed fever with swelling of the face and feet. She was confined to her bed for two weeks at this time. On the third day of the illness a diagnosis of pneumonia was made. About June 28, a severe generalized edema appeared and persisted until death. Admitted to hospital, Aug. 9, 1913. Empyema was recognized, and was drained by rib resection August 15. Urine was scanty and contained many granular, waxy and hyalin casts, and large quantities of albumin. Phenolsulphonephthalein, 39 per cent. August 25;

36 per cent., September 1. Death, September 24. Duration of nephritis about three months. Necropsy: Purulent peritonitis. Pure growth of pneumococci from peritoneal exudate. Empyema. Kidneys cloudy and swollen. Severe glomerulitis; capillaries largely closed by the swollen endothelial cells (Fig. 5). Polymorphonuclears rare in most glomeruli; numerous in a few. A few glomeruli show beginning hyaline degeneration with early tubular atrophy.

Case 23 (A-13-150).—Male, aged 35 years. Illness began three and one-half months before death with frequent chills, fever and vomiting. Became better and went back to work. About one month later he developed a cough with weakness, loss of appetite and pain in the right chest. Admitted to hospital Sept. 18, 1913. Temperature of septic type. Slight edema of both legs. Abundant albumin and many casts in the urine. Leukocytes, 18,000. Death, Oct. 4, 1913. Necropsy: double empyema. Kidneys swollen and cloudy. Glomeruli are not enlarged but the capillaries contain large numbers of polymorphonuclear leukocytes. These cells are also found occasionally in the tubules and in the interstitial tissue. There is very little swelling of the glomerular endothelium. This may be considered an exudative glomerulitis.

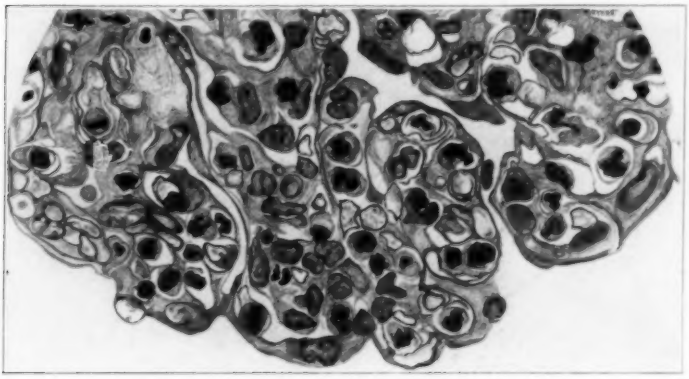

Fig. 3.—Case 17. Acute exudative glomerulitis. Note the polymorphonuclears. There is some enlargement of the endothelial cells.

Case 24 (A-13-153).—Female, aged 13 years. Developed a sore throat, Sept. 22, 1913. This continued with some improvement until September 28 when there was frequent emesis, anorexia and malaise. September 30 there were definite symptoms of peritonitis, and two days later a laparotomy revealed seropurulent peritonitis. Many streptococci were shown in smears of the exudate. Leukocytes, October 2, 24,000. During the next five days there was a very small amount of urine. Each specimen contained abundant albumin, blood and many casts. There was no edema. Death, Oct. 7, 1913. Necropsy: Purulent peritonitis; great enlargement of spleen and kidneys. Glomeruli are all enlarged and the capillaries are for the most part closed by the swollen endothelial cells (Figs. 6 and 7). There are many polymorphonuclears in some of the glomerular capillaries, and there are large numbers of them in the lumina of the tubules. There is severe tubular injury and many tubules are filled with blood. Many mononuclear leukocytes are seen in the interstitial tissue. There is no tubular atrophy. The total duration of the illness was only fifteen days.

Case 25 (A-15-144).—Female, aged 6 years. April 28, 1915, child was dull and tired and had lost her appetite. Severe diarrhea and vomiting for the

next six days. No edema. Convulsions, May 7. Urine: marked albuminuria; hyalin, granular, waxy, pus and blood casts. Leukocytes, 10,600; erythrocytes, 2,400,000. Death, May 7. Necropsy: No anasarca. Edema of lungs. Kidneys weighed 175 gm.; very cloudy cortices. Severe tubular degeneration and necrosis of many tubules. Large numbers of casts. Glomeruli are not enlarged but many of them show extensive hyaline, granular, hydropic and fatty degeneration and occasionally some necrosis of the endothelium. These changes are due to thromboses of the afferent glomerular arteries. Rarely a mitotic figure is seen in the endothelium. This case may be considered a severe nephrosis, since the changes are almost entirely degenerative in character.

Case 26 (A-15-165).—Male, aged 55 years. Illness of about six weeks' duration. Began with severe pain in the chest, dyspnea, edema of legs and anorexia. Urine: abundant albumin, hyalin and granular casts, leukocytes and erythrocytes. Temperature about 100 F. Necropsy: Marked anasarca, ascites and hydrothorax. Edema of lungs. Heart weighed 410 gm. No focus of

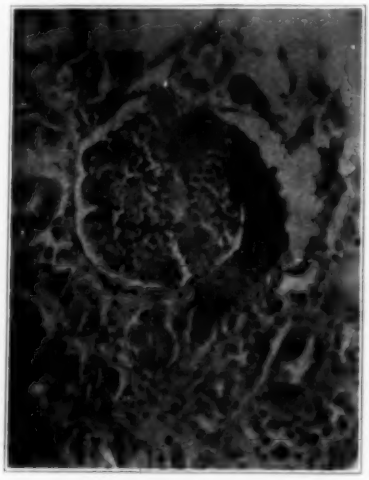

Fig. 4.—Case 20. Degenerative glomerulitis. Thrombosis of afferent artery.

infection found. Kidneys not enlarged, but cortices are grayish yellow. Glomeruli are all enlarged. Enormous increase of nuclei. Almost complete obliteration of all glomerular capillaries. Many polymorphonuclears mark the position of the capillaries. No tubular atrophy.

Case 27 (A-17-176).—Female, aged 66 years. Severe bronchitis first week of August, 1917. This was followed by dyspnea, precordial pain, vertigo and general weakness. Gradual increase in severity of symptoms. On admission to hospital, Aug. 25, 1917, there was edema of the feet. Urine, August 28 and September 6, contained a large amount of albumin and many casts of all types. August 28, leukocytes, 17,000; 94 per cent. polymorphonuclears. Blood pressure, August 30, 220/180; September 6, 200/80. August 29: urea nitrogen 72; creatinin 1.7. August, 31, urea nitrogen 46.5; creatinin 2.5. Phenolsulphonephthalein, August 31, 27 per cent.; September 6, 12 per cent. Death, September 8, 1917. Necropsy: a large amount of seropurulent fluid in each pleural cavity. Small areas of bronchopneumonia. Heart, normal. Kidneys weighed 300 gm.; cloudy surfaces. Glomeruli are all moderately enlarged.

There is a notable increase in the number of nuclei. Nearly all the capillaries are completely closed by swollen endothelium. Many disintegrating polymorphonuclears are seen in the positions of the closed capillary lumina. The tubules connected with a few of the glomeruli show a definite early stage of atrophy. The glomeruli are not all injured to the same degree; a few have a number of permeable capillaries. Duration of illness about one month.

Case 28 (A-18-62).—Male, aged 27 years. Right kidney removed February 21. This kidney showed tuberculosis but no glomerulonephritis. Extensive suppuration of the surgical wound developed. Septic temperature. Urine: March 10 and March 14, large amount of albumin, pus and casts. Erysipelas appeared April 1. Death, April 2. Necropsy: edema of left leg. Enormous dissecting abscess of abdominal wall extending from the surgical wound. A small amount of excess fluid in the serous cavities. Left kidney weighed 290 gm. Cortex opaque with yellowish and reddish mottling. A majority of the malpighian bodies show epithelial crescents which compress the glomeruli (Fig. 8). There is very little swelling of the endothelium. There are large numbers of polymorphonuclears in the glomeruli, capsular spaces, and surrounding the malpighian bodies. There is severe tubular degeneration. This is the extracapillary type of glomerulonephritis.

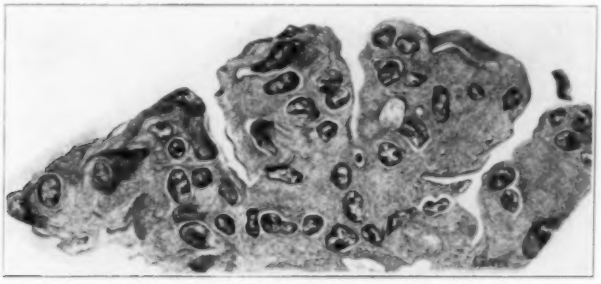

Fig. 5.—Case 22. Acute proliferative glomerulitis—small portion of a glomerulus. Note complete obliteration of the capillaries.

Case 29 (A-18-251).—Female, aged 18 years. Admitted to hospital Nov. 27, 1918. Septic temperature. Severe prostration. Peritonsillar abscess. Abscess was opened November 27 and again November 28. There was erysipelas of the face on admission and the entire face was involved before death. Blood pressure, 96/54. November 27, 2 ounces of urine was removed by catheter. November 28, 1 ounce removed by catheter. Urine contained a large amount of albumin with enormous numbers of casts. Death, December 1. Necropsy: Slight edema of ankles. No fluid in the serous cavities. Heart not enlarged. Extensive bronchopneumonia. Hemolytic streptococcus from the blood. Kidneys weighed 540 gm. Cortices were swollen and very cloudy. All the glomeruli are moderately enlarged. There is a little swelling of the endothelium. There are large numbers of polymorphonuclears in the glomeruli capillaries, in the capsular spaces, and in the tubules. There is severe tubular injury.

Case 30 (A-19-152).—Male, aged 12 years. Attack of smallpox about the middle of June, 1919. Has had edema of the face and extremities ever since. Vomiting and convulsions July 18. Admitted to hospital July 19. Dyspnea. Frontal headache. Râles throughout the chest. Dulness over right lower lobe. Leukocytes, 19,800; 94 per cent. polymorphonuclears. Blood pressure, 132/94.

Urine: abundant albumin, many granular and epithelial casts. Death, July 21, 1919. Necropsy: Ascites (500 c.c.); hydrothorax (each cavity about 1,000 c.c.), edema of face. Heart weighed 200 gm. Small areas of bronchopneumonia. Spleen weighed 220 gm.; kidneys, 245 gm. Swollen, cloudy cortices. All glomeruli enlarged. Nearly all the capillaries closed by swelling of the endothelium. Very few polymorphonuclears. Severe tubular injury. No tubular atrophy.

Case 31 (A-21-62).—Female, aged 7 weeks. A few days after birth the mother noticed puffiness of the eyelids which gradually increased. On the eighth day there was a profuse purulent discharge from the eyes with swelling of the lids. This discharge continued. When the child was 5 weeks old it was brought to the university dispensary for treatment. No gonococci were found. Some improvement under treatment. February 4, the mother first noticed swelling of the face, hands and neck. Admitted to hospital, Feb. 7, 1921. General anasarca. Systolic murmur at base of heart. No convulsions. No

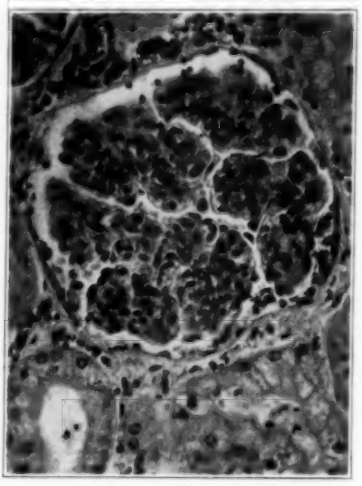

Fig. 6.—Case 24. Proliferative glomerulitis, intracapillary type. Low magnification. Note solid lobules, also polymorphonuclears in lumina of tubules.

spasticity of muscles. Phenolsulphonephthalein, a trace. Creatinin, 4.25 mg.; urea nitrogen, 29.16 mg. Very little urine excreted. A few drops removed by catheter showed hyalin, granular, epithelial and erythrocyte casts. Hemoglobin, 63 per cent. Leukocytes, 24,800; 30 per cent. polymorphonuclears; 65 per cent. lymphocytes. Temperature from 97 to 98.6 F. Death Feb. 14, 1921. Acute fibrinopurulent pleuritis of right side. Infected infarct of right lung (streptococci in smears). Streptococcus in pure culture from heart's blood. Kidneys weighed 50 gm. Cloudy yellowish cortices. Smooth external surfaces. Extensive involvement of nearly all the glomeruli. The capillaries are closed, and there is beginning hyaline degeneration in many glomeruli. There are very few polymorphonuclears. There is beginning tubular atrophy.

Case 32 (A-20-215).—Male, aged 60 years. Admitted to hospital May 25, 1920, in coma. Temperature as high as 105 F. Blood pressure, 160/80. Urine: specific gravity 1020; moderate amount of albumin; many erythrocytes; many granular casts. Leukocytes, 21,000; 70 per cent. polymorphonuclears. Blood

chemistry: creatinin, 5.8 mg.; urea nitrogen, 86.2 mg.; sugar 0.19 per cent. Death, May 26, 1920. Necropsy: ascites (300 c.c.). Heart weighed 350 gm. Edema of lungs. Extensive ulcerative colitis. Kidneys weighed 305 gm.; cloudy cortices. Severe degenerative changes in both tubules and glomeruli. Very slight evidence of reaction in glomeruli. This may be considered a severe nephrosis.

The Clinical Phenomena in Acute Glomerulonephritis.—In twenty-one of the thirty-two cases, the renal symptoms were so masked by the associated disease that a diagnosis of nephritis would have been very difficult; and in Cases 1 to 9 the involvement of the kidneys was

Fig. 7.—Case 24. Acute glomerulitis, proliferative and exudative. Note swelling and increase of endothelial cells with closure of capillaries. There are a number of polymorphonuclears.

probably too slight to produce any prominent findings. Cases of this kind are, of course, not ordinarily considered as Bright's disease by the clinician; but they are very valuable in the study of the early stages of the disease, since the changes in the kidneys are of the same type as those of typical clinical acute Bright's disease.

Considering only the eleven typical cases (Cases 22 to 32), it will be noted that eight showed edema of some part of the body. In Cases 24, 25 and 32, edema was absent. All showed heavy albuminuria and numerous casts, usually granular. Renal function was tested in four patients. Cases 27 and 31 showed a slight, and Case 32 a marked

retention of metabolites in the blood. The phthalein elimination was found decreased in Cases 22, 27 and 31. The phthalein measurement in Case 31 is not consistent with the blood chemistry and was probably incorrectly determined because of the very small amount of urine excreted. The duration is difficult to determine in many instances but seems to vary from a few days to three months. In only three patients (Cases 25, 26 and 30) did death seem to be due mainly to renal involvement; in the other eight cases there were very severe complicating infections. The data as to age and sex have little value because of the small number of cases.

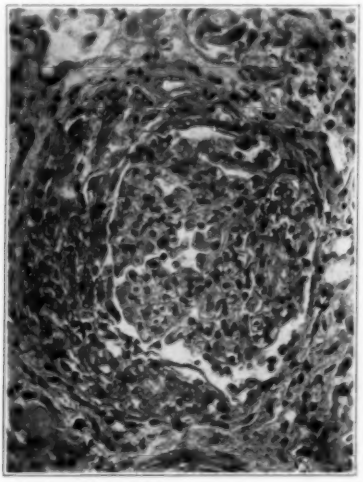

Fig. 8.—Case 28. Fresh epithelial crescent.

Gross Changes in the Kidneys.—With the exception of the very mild cases the cortices are invariably cloudy, and in the more severe cases the cloudiness and opacity are very pronounced and sometimes a yellowish tinge can be detected. The kidneys are not always enlarged. In general, the enlargement is proportional to the severity, but occasionally severe injury is found in kidneys of normal weight (Cases 26, 27 and 32). Among seventeen adults whose weights are recorded there are eight cases in which the kidneys weighed more than 400 gm., and four weighed more than 500 gm. The single kidney in Case 28 weighed 290 gm. It is apparently not possible to distinguish a nephrosis from acute glomerulonephritis by the gross appearance.

The Normal Glomerulus.—Before studying the glomerular changes in acute nephritis attention should be directed to the structure of the

normal glomerulus. The microscopic appearance of a glomerulus varies with the amount of blood it contains. When distended, the lumina of the capillaries are large, their endothelial walls are thin and the individual capillaries are fairly distinct. When empty, the endothelial walls of the capillaries are thicker, their lumina are very small or even invisible, and it may not be possible to see the individual capillaries. The glomerulus is, of course, much larger when distended than when empty. In necropsy material the great majority of the glomeruli ordinarily contain only a little blood; and it is often difficult in disease to distinguish an empty capillary from one in which the lumen has been closed by endothelial swelling. Thin sections of well fixed material are necessary for the study of glomerular structure.

Fig. 9.—Case 55. Chronic case. Section through entrance of artery. Note lobules. A few polymorphonuclears are visible at the site of closed capillaries.

The glomerulus is composed almost entirely of capillary loops which anastomose freely. The arrangement of the capillaries is shown well in Johnston's [6] reconstruction. Corresponding with the capillary loops, the glomerulus is subdivided into a number of small lobules which have their narrow apex in common near the point of entrance of the artery and their wider bases free at the periphery. This lobulation is best seen in diseased glomeruli where there has been some shrinkage but is sometimes visible in the normal. The lobulation is well shown in Figure 9 in a section through the entrance of the artery. In ordinary histologic

6. Johnston, W. B.: A Reconstruction of a Glomerulus of the Human Kidney, Anat. Anzeiger **16**:260, 1899.

preparations no connective tissue is visible between the capillaries, but Johnston was able to demonstrate fine reticulum fibrils. These fibrils apparently do not take any part in inflammations of the tuft.

In Figure 10 a small part of a normal congested glomerulus is shown under high magnification. Most of the capillaries are distended with erythrocytes, and the endothelial cells appear as thin plates where the plane of the section is about perpendicular to the course of the vessel.

The capsule of Bowman lines the outer wall of the capsular space and is reflected over the glomerulus. The inner layer is prominent in infancy but apparently does not form a continuous layer in the adult kidney. Some of the cells of this layer are found in the clefts between the glomerular lobules (Fig. 10). It is often prominent in shrunken

Fig. 10.—Normal congested glomerulus. Note the thinness of the endothelium when the capillaries are distended.

glomeruli. The outer layer takes a prominent part in the extracapillary type of lesion which will be described below.

THE GLOMERULUS IN ACUTE INFLAMMATIONS.—The three fundamental phenomena of inflammation, viz., degeneration, exudation and proliferation—occur in the glomerulus as they do in other tissues and their relative prominence determines the microscopic appearance. The peculiar structure of the glomerulus, however, influences markedly the course and outcome of the inflammatory process. In most instances the only fixed tissue concerned is capillary endothelium and the occlusion of capillaries produces permanent damage that seems out of proportion to the intensity of the injury. In accordance with the prominence of the fundamental processes three types of glomerulitis may be described.

(*a*) *Degenerative Glomerulitis.*—In this form there is disintegration and necrosis of the glomerular endothelium with escape of blood into the capsular space. It is usually associated with severe tubular injury

also. The reactive changes are very slight. Case 32 is a good example of a severe case with involvement of all the glomeruli. In Cases 25 and 20 the degenerative changes are largely due to thrombosis of afferent arteries and many glomeruli escaped serious injury (Fig. 4).

Mild degenerative changes may be responsible for a hematuria. Figure 11 is from a case of severe hematuria apparently due to a bacteremia. A large percentage of the glomeruli show a similar appearance. The blood escapes from ruptured capillaries but the glomerulus as a whole shows no signs of permanent injury. It is possible that some of the cases in children described by Hill[7] as hemorrhagic nephritis have only trivial glomerular injuries such as this. Hill states

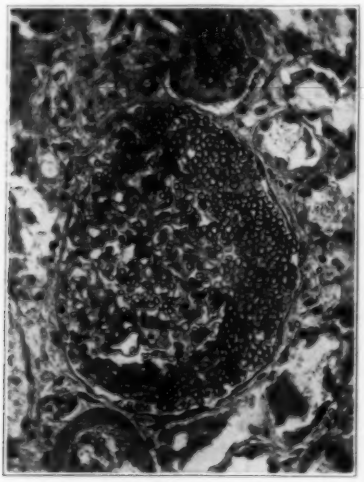

Fig. 11.—Degenerative glomerulitis. No permanent renal injury. From a case of bacteremia with severe hematuria.

that these cases have an especially favorable prognosis. Renal hematuria does not necessarily indicate a serious glomerular injury. A few erythrocytes in the urine may be due to passive congestion or to mild injuries such as occur in any nephrosis.

(*b*). *Exudative Glomerulitis.*—This type is characterized by the appearance of an unusual number of polymorphonuclear leukocytes in the glomerular capillaries. The leukocytes pass through the capillary walls into the capsular space and are carried away in the urine. There is usually an associated swelling of the endothelium but in seven of

7. Hill, L. W.: Studies in the Nephritis of Children, Am. J. Dis. Child. **17**:270 (April) 1919.

our cases this is inconspicuous and the lesions are mainly exudative. Some polymorphonuclears were found in the glomeruli in nearly all our cases of glomerulitis, but in ten of them they were very rare. Figure 3 (Case 17) is a good example of an exudative glomerulitis. There is apparently no narrowing of the capillary lumina in this case and it does not appear that any serious permanent damage has been done. Possibly the plugging of the capillaries with leukocytes may interfere with function to some extent. It is an attractive hypothesis that mild cases of acute Bright's disease are of the exudative type, but there are no supporting observations. We do know, however, that our severe clinical cases were either mainly proliferative or mainly degenerative.

Fig. 12.—Case 47. From a chronic case. Low magnification. Note polymorphonuclears in the solid lobules. See Figures 13 and 14.

When acute cases become chronic the leukocytes remain permanently in the occluded capillaries and remnants of them are recognizable for a long time (Figs. 12, 13, 14). This feature helps to establish the relationship between the acute and the chronic case.

In one instance (Case 16) the exudate was so abundant that a number of glomeruli were converted into small abscesses (Fig. 2). The other glomeruli showed the changes characteristic of typical glomerulonephritis. There was a large amount of exudate in the interstitial tissues also. This case shows the close relationship between the pyelonephritis group and glomerulonephritis, and furnishes an argument in favor of the infectious nature of the latter disease.

(*c*) *Proliferative Glomerulitis.*—Occurs in two forms: the extracapillary and the intracapillary. The extracapillary type consists in proliferation of the cells of the outer layer of Bowman's capsule. These newly formed cells usually become arranged in the form of a crescent (Fig. 8), which compresses the glomerulus and ultimately causes it to undergo atrophy and hyaline degeneration. The epithelial crescent itself finally undergoes hyaline degeneration but remnants of nuclei are visible for a long time. The presence of old epithelial crescents in a chronic case (Fig. 15) suggests an acute beginning. Extracapillary lesions are not frequently seen. They were found in only two of our acute cases (Cases 16 and 28). According to Volhard and Fahr they occur especially in infections with violent onset, and this view is sup-

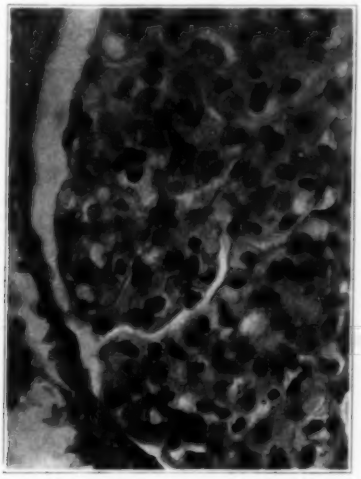

Fig. 13.—Case 47. High magnification of Figure 12. Polymorphonuclears are visible in the solid lobules at the site of capillaries which have been closed by swelling of their endothelium.

ported by our cases, Case 28 being the most severe infection of the entire series.

The intracapillary type is the most common and the most important form of glomerulitis. It consists in swelling of the endothelial cells and increase in their number. The glomerulus as a whole is enlarged and there is usually a notable increase in the number of nuclei. Rarely a mitotic figure is seen. More important than the increase in the number of the endothelial cells is their increase in size. The capillary lumina are obliterated so that entire lobules may appear solid (Fig. 5). Low power views of the acute stages in the glomeruli are shown in Figures 1 and 6, and high power views of a few lobules are seen in Figures

5 and 7. Polymorphonuclear leukocytes are frequently present, occasionally in large numbers (Fig. 7); but some times they are absent entirely from large portions of the glomerulus (Fig. 5). These leukocytes are frequently seen also in the lumina of the tubules (Fig. 6), and in the interstitial tissue (Fig. 16). They are often caught in the closed capillaries where they are easily recognized in subacute stages before hyaline degeneration of the glomerulus begins (Figs. 12, 13 and 14); and they may be seen by careful examination in many chronic stages (Figs. 9 and 17). This microscopic feature furnishes an important connecting link between acute and chronic glomerulonephritis. As a result of intracapillary glomerulitis, the entire capillary network of the tuft may be closed completely, in which event the glomerulus undergoes hyaline degeneration and its tubule atrophies to the point of complete disappearance. Frequently, however, some of the capillaries are not occluded (Fig. 17), and the glomerulus continues to function to a limited extent, in which event only a partial atrophy of the associated

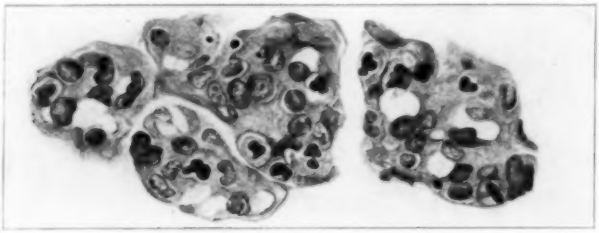

Fig. 14.—Case 47. See Figures 12 and 13. High magnification, showing remnants of polymorphonuclears in the solid lobules. Capillaries are largely obliterated by growth of endothelial cells.

tubule occurs. This type of damaged glomerulus is very common in chronic glomerulonephritis.

The tubules in acute glomerulonephritis usually show some degenerative changes. An increased amount of fat is often demonstrable; and hyaline granular degeneration is occasionally seen. In the degenerative type there may be some necrosis. As soon as the glomerulus ceases to function the tubule begins to atrophy, but this is never marked in an acute case. In Cases 27 and 31 atrophy of tubules had begun.

The interstitial tissues frequently show an exudate of mononuclear or polymorphonuclear leukocytes (Fig. 16). This exudate, however, does not seem to destroy any tubules and probably does not affect the course of the disease to any noteworthy extent.

ETIOLOGY OF ACUTE GLOMERULONEPHRITIS

The prevailing opinion in the literature is that acute glomerulonephritis is closely associated with infectious processes. Our experience

is entirely in accord with this view. Table 1 gives the associated infections found at necropsy or determined clinically in our thirty-two cases. The numbers refer to the individual cases. It will be noted that some of the patients had more than one infection.

The frequency of acute endocarditis in our series is very impressive —twelve times in thirty-two cases, or 37.5 per cent. In seven of these hearts the valve leaflets showed chronic changes also, so that these are to be regarded as acute exacerbations of a chronic endocarditis. That the frequent association of these two conditions is not accidental

TABLE 1.—Associated Infections in Cases of Acute Glomerulonephritis

Associated Infections	*Cases*
Vegetative endocarditis	1,2,3,5,10,11,12,13,14,16,19,21
Puerperal sepsis	6
Empyema, or purulent pleuritis	7,20,22,23,27
Peritonitis	20,22,24
Streptococcic bacteremia	4,7,8,17,29,31
Pneumococcic bacteremia	9,20
Septic sore throat	7,24,29
Erysipelas	4,28,29
Lobar pneumonia	8,12
Suppurative otitis media	7
Suppurative pharyngitis	9
Streptococcic arthritis and osteomyelitis	4
Infected surgical wound	28
Meningitis	7
Acute arthritis (not present at time of death)	10,11,13,16
Severe bronchitis	27
Variola	30
Tuberculosis with cavities	15
Ulcerative colitis	32
Diabetic gangrene	17
Purulent conjunctivitis	31
No localized infection	6,18,25,26

is shown by the fact that in our 3,300 consecutive necropsies, not including those with acute nephritis, there were only sixty-three with acute endocarditis, or only 1.9 per cent.

This relationship has been observed by others. Leyden [8] noted the association of rheumatism, endocarditis and nephritis. Councilman [9] found ten instances of acute endocarditis in twenty-eight cases of acute nephritis. Klotz [10] also found endocarditis and nephritis in frequent association. Ophüls [11] cites three cases of acute nephritis associated with acute exacerbations of a chronic endocarditis.

8. Leyden, Cited from Mannaberg.[18]

9. Councilman, W. T.: An Anatomical and Bacteriological Study of Acute Diffuse Nephritis, Am. J. M. Sc. **114**:23, 1897.

10. Klotz, O.: Chronic Interstitial Nephritis and Arteriosclerosis, Am. J. M. Sc. **150**:832, 1915.

11. Ophüls, Wm.: A New Series of Cases with a Review of Recent Literature, Stanford Univ. Med. Bull. No. 3, 1915.

Four cases in our series gave a history of rheumatic fever prior to the terminal illness, and several writers seem to consider this disease closely related to acute nephritis.

The relation of tonsillitis to acute glomerulonephritis has been discussed by a number of investigators. Kannenberg [12] in 1879 reported three cases of tonsillar infections (two were peritonsillar abscesses) followed by acute nephritis. In one cases the urinary changes appeared on the seventh day. Mannaberg [13] mentions tonsillitis among the infections sometimes followed by Bright's disease. Bluhm [14] reported

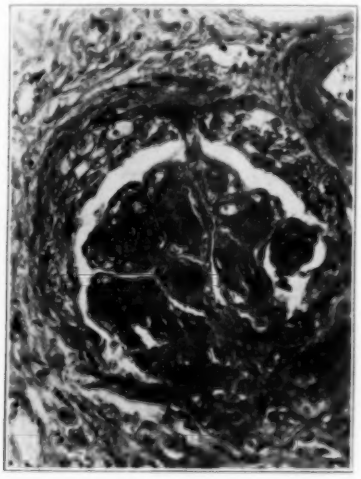

Fig. 15.—Case 56. Old epithelial crescent. Compression of glomerulus with beginning hyaline degeneration.

that five out of seventy-four cases of tonsillitis developed Bright's disease. Löhlein [15] and Aschoff [16] mention angina among the causes of glomerulonephritis. Volhard and Fahr [1] attribute to angina seventeen out of seventy-one acute, and seven of thirty-two subacute cases. In one instance cited by these authors nephritis appeared fourteen days

12. Kannenberg: Ueber Nephritis bei acuten Infectionskrankheiten, Ztschr. f. klin. Med. **1**:506, 1879.

13. Mannaberg, J.: Zur Aetiologie des Morbus Brightii acutus, etc., Ztschr. f. klin. Med. **18**:223, 1890.

14. Bluhm, A.: Zur. Aetiologie des Morbus Brightii, Deutsch. Arch. klin. Med. **47**:193, 1891.

15. Löhlein, M.: Ueber Nephritis nach dem heutigen Stande der path.-anat. Forschung, Ergeb. der inn. Med. u. Kinderh. **5**:411, 1910.

16. Aschoff, L.: Pathologische Anatomie, **2**:483, 1921.

after an attack of sore throat. Ophüls [17] attaches great importance to tonsillar infection as a source of glomerulonephritis, and Herxheimer [18] seems to hold a similar view. Hill [19] found tonsillitis the most frequent cause of nephritis in children, and James' [20] observations are in agreement with those of Hill. Hill states that the renal symptoms usually appear about one week after the tonsillar infection.

Evidently there is a close relationship between tonsillitis, endocarditis, arthritis and acute glomerulonephritis. It seems probable from all the accumulated evidence that the pathogenic bacteria gain access

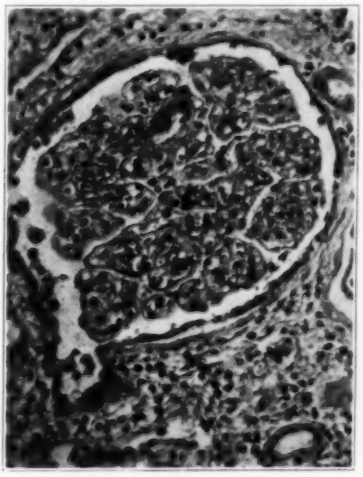

Fig. 16.—Case 43. From a chronic case. The capillary network of the lobules is largely closed. Many polymorphonuclears in the interstitial tissues.

to the blood stream from an infected throat and that the subsequent clinical picture depends on whether they attack the heart valves, joints or glomeruli.

There were three cases of septic sore throat in our series, and there were ten cases with acute endocarditis in which the throat was a possible source of the infection.

17. Ophüls, Wm.: The Etiology and Development of Nephritis, J. A. M. A. **69**:1223 (Oct. 13) 1917.

18. Herxheimer, G.: Ueber den jetzigen Stand unserer anatom. Kenntnisse der Nephritis u. Nephropathien, Münch. med. Wchnschr. **65**:283, 1918.

19. Hill, L. W.: Acute Nephritis in Childhood, J. A. M. A. **73**:1747 (Dec. 6) 1919.

20. James, R. F.: Prognosis of Nephritis in Childhood, J. A. M. A. **76**:505 (Feb. 19) 1921.

Scarlet fever was one of the first diseases in which a relationship to nephritis was observed. According to Friedlander [21] post-scarlatinal glomerulonephritis was first described by Klebs. Urinary disturbance occurs in from 20 to 25 per. cent. of cases of scarlet fever (McCrae,[22] 25 per cent. of 1,034 cases; Sorensen,[23] 20 per cent. of 365 cases). But the abnormal urine is usually due to acute interstitial nephritis or nephrosis. Only 2 per cent. of McCrae's patients had physical signs and symptoms of a true nephritis. Friedlander, Sorensen and others believe that true glomerulonephritis usually develops in the convalescent stage, during the third or fourth week after the onset of the disease.

Fig. 17.—Case 43. A common form of damaged glomerulus in chronic glomerulonephritis. Some capillaries are closed but many are permeable. The tubule associated with this glomerulus showed moderate atrophy.

In fatal cases of scarlet fever glomerulonephritis is frequently seen (Friedlander, in 18 per cent. of 229 necropsies; Reichel,[24] in 29 per cent. of fifty-eight necropsies). Aschoff considers scarlet fever a frequent cause of glomerulonephritis. Volhard and Fahr found nineteen of seventy-one acute cases, and two of thirty-two subacute cases due to scarlet fever. The older observers considered the glomerular

21. Friedlander, C.: Ueber Nephritis scarlatinosa, Fortschr. d. Med. **1**:81, 1883.

22. McCrae, J.: Incidence of Nephritis Following Scarlet Fever, Tr. Assn. Am. Phys. **28**:194, 1913.

23. Sorensen, S. T.: Ueber Scharlachnephritis, Ztschr. f. klin. Med. **18**:298, 1890.

24. Reichel, H.: Ueber Nephritis bei Scharlach, Ztschr. f. Heilk. **6**:72, 1905.

injury due to poisonous substances excreted by the kidneys, but recent investigators attribute it to streptococcic infection.

There are no cases in our series in which a history of scarlet fever was obtained.

One of our cases followed an attack of variola, but apparently this is not a common cause since Bluhm found only one case of Bright's disease among 481 cases of variola.

Lobar pneumonia appears twice in our series as a possible source of infection; but Councilman found glomerulonephritis only once in 107 cases of pneumococcus pneumonia.

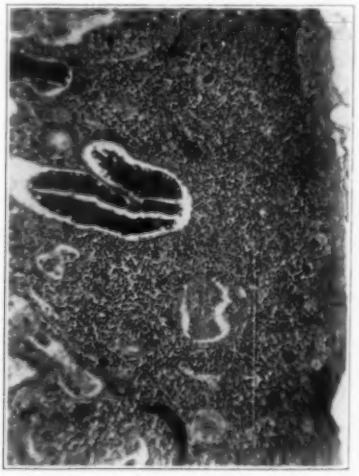

Fig. 18.—Case 51. Chronic case six years after an attack of scarlet fever. These areas are probably the result of an acute interstitial nephritis during the attack of scarlet fever.

Three of our series were associated with erysipelas and Bluhm found Bright's disease seven times in 162 cases of erysipelas. This disease is mentioned by several observers as a cause of acute Bright's disease.

A large number of other infections, some of which appear in our series, are mentioned by various investigators as having a causal relationship to acute glomerulonephritis. Among these are infected wounds, puerperal sepsis, peritonitis, empyema, impetigo, osteomyelitis, tuberculosis with cavities, otitis media, etc. Gaskell [25] describes a case

25. Gaskell, J. F.: On the Changes in the Glomeruli and Arteries in Inflammatory and Arteriosclerotic Kidney Disease, J. Path. & Bacteriol. **16**:287, 1911.

of less than one week's duration following peritonitis. McElroy[26] cites a characteristic case developing two or three weeks after a severe infection of one hand. Cases such as these are apparently frequent in the practice of many clinicians, and there are probably few of wide experience who have not seen a case of acute Bright's disease that followed some infectious process.

The various infections which apparently cause acute glomerulonephritis are generally due to streptococci, less frequently to pneumococci. In scarlet fever it is believed that a streptococcic infection of the throat develops in the period of convalescence, which gives rise to the renal involvement. Löhlein, Volhard and Fahr, Aschoff and Ophüls

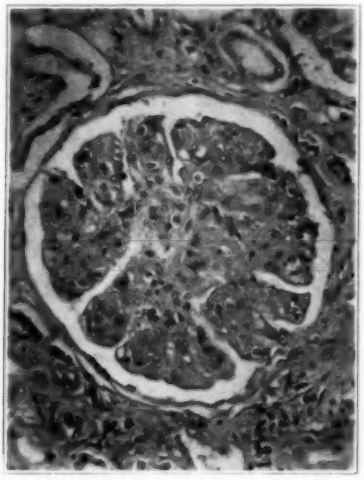

Fig. 19.—Case 53. Chronic case, showing almost complete occlusion of all the capillaries. No hyaline degeneration. Marked atrophy of associated tubule.

all agree that streptococci are chiefly responsible for acute glomerulonephritis. Ophüls apparently believes that other bacteria, e. g., *B. influenzae* and *B. coli*, may occasionally produce this disease.

In our series there were six cases with streptococcic bacteremia. In three of these the organisms were hemolytic; but there is no record as to the type in the other three cases. Nonhemolytic streptococci have not been found in our cases of acute glomerulonephritis, but they have been cultured from the blood in several cases of embolic glomerulonephritis. Further study is necessary to determine whether the nonhemolytic strains are ever responsible for acute Bright's disease.

26. McElroy, J. B.: Nephropathies, M. Clin. N. America **1**:1457, 1918.

Two instances of pneumococcic bacteremia appear in our series—one associated with suppurative pharyngitis and bronchopneumonia, the other with suppurative pleuritis and peritonitis.

It has not been determined whether the bodies of the bacteria or some diffusible toxin produces the glomerular injury. In favor of the toxin theory is the absence of bacteria in the glomeruli, and the diffuse uniform character of the lesion—practically all the glomeruli are usually involved. A few of the earlier workers described bacteria in the glomeruli, but Ophüls has pointed out that more recent contributors by careful histologic examination have failed to find bacteria in the glomerular endothelium. Sections from ten of our acute cases were

Fig. 20.—Case 56. Chronic case, showing complete closure of capillaries and beginning hyaline degeneration. Lobules are very distinct. Note disintegrated polymorphonuclears in the lumina of the tubules.

stained by the Gram-Weigert method, but no bacteria were found in the endothelium. However, in sections from an acute case following erysipelas, which were furnished us by Dr. J. P. Schneider, large numbers of gram-positive cocci were easily seen in the swollen endothelial cells of the glomerular capillaries. Ophüls has suggested that the bacteria undergo rapid lysis in the endothelium and are therefore seldom seen. This view is supported by Pappenheimer, Hyman and Zeman,[27] who injected bacteria directly into the renal artery of the

27. Pappenheimer, Hyman and Zeman: Acute Glomerular Lesions Following Injections of Bacteria Into the Renal Artery, Proc. New York Path. Soc. **16**:73, 1916.

rabbit. They found that the bacteria were taken up by polymorphonuclears and endothelial cells in the glomeruli within a few minutes and that within four hours they had nearly all undergone complete intracellular digestion.

War nephritis is anatomically acute glomerulonephritis, according to all who have studied necropsy material. It differs clinically in its epidemic character. Several observers have noted a frequent association with infectious processes (Brown,[28] Tytler and Ryle,[29] Ameuille [30]); but all seem to agree that a localized primary infection is not demonstrable in a majority of cases. Streptococci have been demonstrated in the

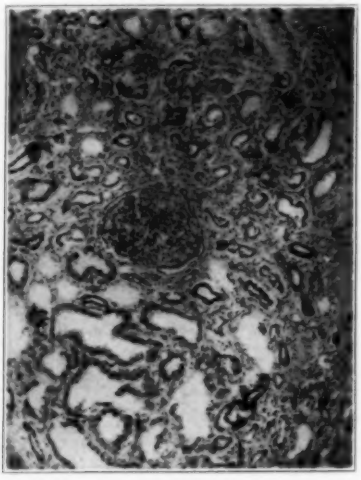

Fig. 21.—Case 60. Typical chronic case, low magnification. The larger tubules on the left are connected with a glomerulus that has a number of permeable capillaries.

urine but they may have been secondary invaders. No satisfactory etiologic studies have been reported.

SUBACUTE AND CHRONIC GLOMERULONEPHRITIS

The arrangement of our cases into subacute and chronic groups is arbitrary, since these subdivisions are not sharply defined. Cases 33 to 41 may be considered subacute. When the known duration of the disease is over one year it is considered chronic. When as many as

28. Brown, L.: Epidemic Nephritis, Brit. M. J. **2**:723, 1916.

29. Tytler and Ryle: Clinical and Pathologic Notes on Trench Nephritis, Quart. J. M. **11**:112, 1917.

30. Ameuille, P.: Du role de l'infection dans les néphrites de guerre, Ann. de méd. **3**:298, 1916.

ten per cent. of the glomeruli have become complete hyalinized and their tubules show advanced atrophy, the case is considered chronic, since the study of cases of known duration has shown that a long time is required for this change to occur. But the rate of tubular atrophy is not the same in all cases and it is probable that this feature is not an accurate index of the duration of the disease.

CASE 33 (A-12-131).—Male, aged 33 years. Admitted July 17, 1912. About one month before admission he developed dyspnea which was increased by exertion and gradually became worse. One week before admission his feet began to swell and dyspnea became very alarming. On admission he com-

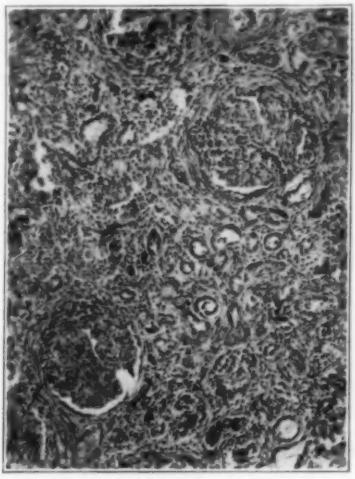

Fig. 22.—Case 69. Chronic case, showing old epithelial crescents, atrophied tubules and interstitial exudate.

plained of precordial pain, cough, dyspnea, and swelling of the feet. The urine contained albumin at all times. The specific gravity was 1.030 July 18; 1.012 September 8. Death, Oct. 7, 1912. Necropsy: Edema of ankles, moderate ascites and hydropericardium; edema of lungs. Heart weighed 460 gm.; moderate thickening and retraction of the mitral and aortic leaflets. Kidneys weighed 415 gm.; cloudy cortices; smooth external surfaces. The glomeruli are all involved but in varying degrees. There are a number of epithelial crescents which compress the glomeruli. Most of the glomeruli show swelling of the endothelium with partial or complete closure of the capillaries but none of them show any hyaline changes. Nearly all the tubules are moderately atrophic. A few polymorphonuclear leukocytes are seen.

CASE 34 (A-13-8).—Female, aged 26 years. Attack of pericarditis in October, 1912. The pericarditis cleared up but hematuria appeared and persisted. Readmitted to hospital Dec. 23, 1912. Edema was never very prominent. Blood and casts were continuously present in the urine. Toward the end of her illness there was severe hematuria and hemorrhages from the vagina and mouth. Death Jan. 10, 1913. Necropsy: No edema; ascites (200 c.c.). Heart not

enlarged. Kidneys not enlarged. External surfaces smooth. Cortices cloudy. Glomeruli are all involved. The great majority show epithelial crescents with compression of the tufts. Some show endothelial swelling with closure of the capillaries. There are numerous polymorphonuclears in some glomeruli. Many tubules and capsular spaces are filled with blood. Numerous mononuclear leukocytes (mainly plasma cells) are seen in the interstitial tissues. Nearly all the tubules show notable atrophy. No hyaline glomeruli.

Case 35 (A-16-223).—Infant, aged 6 months. Normal at birth. At end of fourth month developed pallor, slight jaundice and weakness. At end of fifth month (May 29, 1916) was very anemic—hemoglobin 20 per cent.; erythrocytes 2,000,000. Blood stained vomitus and stools. Transfused. Suppuration of the transfusion wound. General anasarca. Urine at various times showed albumin, blood and pus cells. Death, June 26, 1916. Suppurating wound of thigh (site of transfusion). Seropurulent pleuritis. Bronchopneumonia. Kidneys weighed

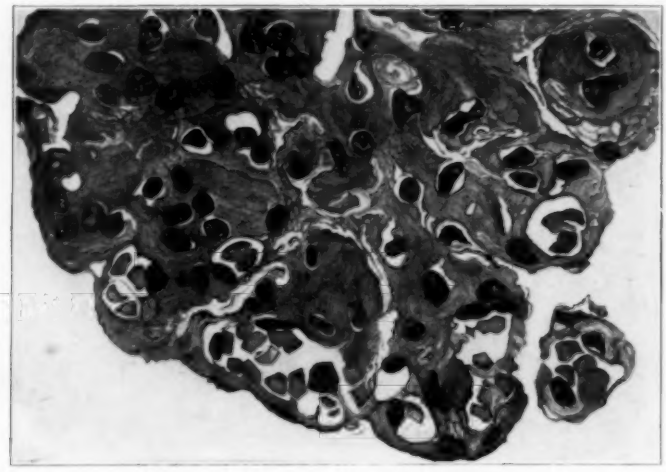

Fig. 23.—Case 53. Chronic case showing only a few permeable capillaries. The associated tubule was very small but had not disappeared.

54 gm.; swollen; pale and cloudy; smooth surfaces. Nearly all the glomeruli show marked swelling of their endothelium with closure of the capillaries. Very few capillaries are patent. There are no hyaline glomeruli. Some tubules are filled with polymorphonuclears, but these cells are very rare in the glomeruli. Tubular atrophy is marked.

Case 36 (A-18-118).—Male, aged 21 years. Syphilitic infection in October, 1917. Treated for three months with mercury injections. One injection of neodiarsenol early in December, 1917. Three days after this injection the patient developed edema with a large amount of albumin, blood and casts in the urine. Phenolsulphonephthalein at this time, 15 per cent.; urea nitrogen, 14 mg.; creatinin, 1.7 mg. December 30, lobar pneumonia developed in right lower lobe. Crisis six days after the attack. April 15, 1918, thrombosis of right popliteal vein developed. Blood pressure at this time was 130/80. Later blood pressure was 140/80. Ascites was present a long time before death. Death, June 2, 1918. Necropsy: Edema of feet and scrotum. Ascites (2,000 c.c.); hydrothorax (1,000 c.c.). Heart weighed 375 gm. Fibrinopurulent pleuritis. Kidneys weighed

425 gm. Cloudy cortices. Smooth external surfaces. Nearly all the glomeruli are severely injured. There is a great increase of nuclei with closure of most of the capillaries, and beginning hyaline degeneration in a few glomeruli. Numerous adhesions between the layers of Bowman's capsule. A few polymorphonuclears in some glomeruli. Rather marked atrophy of tubules.

CASE 37 (A-15-67).—Female, aged 35 years. Appendix, ovaries and tubes removed about seven years ago. Has had swelling of feet for several years. Abdominal paracentesis several times recently. Urine; abundant albumin and casts. Necropsy: marked general anasarca, ascites (3,000 c.c.), hydrothorax (1,500 c.c.) and hydropericardium. Heart weighed 400 gm. Thromboses of pelvic veins with infarction of lungs. Kidneys normal size; surfaces slightly uneven; cortices yellowish. The great majority of the glomeruli are enlarged and show a great increase in number of nuclei. Their capillaries are largely closed by swollen endothelium, and hyaline changes have appeared in many. Many polymorphonuclears are seen in the interstitial tissues and capsular spaces, and there are a few in the closed glomerular capillaries. There is moderate atrophy of most of the tubules. This case appears to be of longer duration than Nos. 33 to 36.

CASE 38 (A-15-253).—Male, aged 51 years. Smallpox at age of 32 years. Well until about April 19, 1915, when he developed a cold with cough following wetting of his feet. There was a yellowish expectoration. About April 26 his face began to swell, and shortly afterwards his legs and abdomen became swollen. There was shortness of breath, headache and some decrease in the amount of urine. Admitted to hospital, May 10, 1915. Blood pressure 172/100. Leukocytes, 13,200. Urine: specific gravity, from 1.020 to 1.030; moderate amount of albumin; casts. Death, Aug. 5, 1915. Necropsy: Pronounced general edema, ascites, hydrothorax and hydropericardium. Heart weighed 375 gm.; kidneys, 500 gm. Smooth external surfaces. A number of glomeruli are completely sclerosed, but these are probably not concerned with his terminal illness. The great majority are somewhat enlarged and their capillaries are largely occluded by endothelial swelling. There is a notable increase in the number of nuclei. No hyalin changes have appeared. There is marked tubular atrophy. Polymorphonuclears are abundant in the interstitial tissues but rare in the glomeruli.

CASE 39 (A-18-237).—Female, aged 22 years. Admitted to hospital, Nov. 1, 1918. A diagnosis of nephritis had been made by a physician three or four months previously, and a therapeutic abortion had been performed about two months before. On admission the patient was in coma and was having convulsions every hour. Albuminuric retinitis was noted. She recovered from the coma but had irrational periods and was stuporous most of the time until her death. There was no urine voided on some days and only from three to six ounces on other days. A friction rub over the heart was heard on November 7. Abdominal paracentesis was performed several times. Blood pressure 220/120. Urine: specific gravity, 1.018; numerous waxy and pus casts, many erythrocytes, large amount of albumin; creatinin, 11.4 mg.; urea nitrogen, 33 mg. Death November 13. Necropsy: Marked anasarca, ascites and hydrothorax. Fibrinous pericarditis. Some pus cells and cocci in plueral and pericardial exudates. Heart weighed 300 gm.; kidneys, 260 gm. External surfaces smooth. Marked atrophy of nearly all the tubules. Very few hyalin glomeruli. Numerous epithelial crescents. Most of the glomeruli show closure of their capillaries with little or no hyaline degeneration. Many disintegrated polymorphonuclears in some of the tubules and in the interstitial tissue.

CASE 40 (A-19-5).—Male, aged 55 years. Was in the hospital about one year ago at which time albumin and casts were found in the urine. There was no edema then. Readmitted, November, 1918. Edema appeared about three weeks before admission. Blood pressure, 200/120. Albuminuric retinitis. Ascites. Phenolsulphonephthalein on admission 20 per cent.; shortly before

death, 0 per cent. Death, January, 1919. Necropsy: Marked general anasarca. Ascites (1,000 c.c.)—fibrinopurulent exudate on a few intestinal coils. Hydrothorax (1,500 c.c.). Edema of lungs. Heart weighed 420 gm.; kidneys, 520 gm. External surfaces smooth. There are very few glomeruli that are completely sclerosed. Nearly all of them show closure of most of the capillaries with beginning hyaline degeneration of the lobules. There are many remnants of polymorphonuclears enclosed in the lobules. A number of epithelial crescents are to be seen. There is moderate atrophy of all the tubules.

Case 41 (A-21-108).—Male, aged 51 years. First admitted to the hospital in October, 1919, with an attack of acute articular rheumatism. The heart was enlarged at this time but the urine was normal. The second admission was Feb. 26, 1921. At this time he had edema of the arms, legs and back, dyspnea and epistaxis. Blood pressure, 228/110. Width of heart 19 cm. Urine: specific gravity, 1.020; large amount of albumin; a few hyalin and granular casts, a few erythrocytes. Hemoglobin, 80 per cent. Erythrocytes, 4,800,000; 16,950 leukocytes—82 per cent. polymorphonuclears. Blood pressure, March 3, 190/100. Ammoniacal odor to the breath. Fever developed during the last few days coincident with the appearance of the physical signs of bronchopneumonia. Death, March 2, 1921. Necropsy: Marked edema of all dependent portions; no ascites; 500 c.c. of thin purulent fluid in the left pleural cavity. Heart weighed 475 gm.; no valvular lesions. Bronchopneumonia. Kidneys weighed 630 gm. External surfaces smooth. No hyalin glomeruli. Large numbers of fairly fresh extra capillary lesions. A great many polymorphonuclears in the swollen glomeruli. Fairly well marked atrophy of nearly all the tubules.

Cases 42 to 45 are apparently intermediate between subacute and well defined chronic cases. The kidneys are not shrunken and there are not many hyalin glomeruli. The tubular atrophy and the hyalinization of the glomeruli are more pronounced than in the previous group. The inflammatory exudate (polymorphonuclears) appears fresher in Cases 42 and 43 than in Cases 44 and 45.

Case 42 (A-16-368).—Male, aged 39 years. Father and one brother died of renal disease. Severe attack of scarlet fever in childhood. Diphtheria at 20. Acute arthritis at 25. Present illness began May 30, 1916, with gastric disturbances and nausea. June 19 he first noticed puffiness of the face, and shortly afterward a general edema developed. Precordial pain for two or three weeks before death. Admitted to hospital in extremis, Oct. 26, 1916. Had generalized edema, ascites, gastric disturbances and precoridal pain. Urea nitrogen, 104 mg.; creatinin, 10.2 mg.; blood sugar, 0.074 per cent.; hemoglobin, 35 per cent. Phenolsulphonephthalein, 0 per cent. Urine: specific gravity, 1.024; abundant albumin, many casts. Leukocytes, 12,000. Death, Oct. 27, 1916. Necropsy: Marked edema of lower half of body; ascites (5,000 c.c.), left hydrothorax (3,000 c.c.), hydropericardium (500 c.c.). Heart weighed 375 gm.; kidneys, 280 gm.; finely granular surfaces. Nearly all the glomeruli show beginning hyaline degeneration. Very few glomerular capillaries are visible. Large numbers of partially disintegrated polymorphonuclears are seen in the closed capillaries and in some of the dilated tubules. There are large numbers of old epithelial crescents. There is advanced atrophy of nearly all the tubules.

Case 43 (A-19-220).—Male, aged 43 years; was well until one year ago when he began to have severe headaches and weakness. He was told by his physician that he had kidney trouble. Admitted to hospital Oct. 2, 1919, complaining of weakness, dyspnea, palpitation of heart, anorexia, precordial pain

and constipation. His heart was enlarged. Blood pressure, 140/60; hemoglobin, 30 per cent.; erythrocytes, 1,300,000; leukocytes, 13,300. Urine: specific gravity, from 1.012 to 1.014; trace of albumin; many granular casts. Phenolsulphonephthalein, October 4, 2 per cent.; October 7, 0 per cent. Blood chemistry: October 7, creatinin, 13 mg.; urea nitrogen, 125 mg.; blood sugar, 0.13 per cent.; October 22, creatinin, 17 mg.; urea nitrogen, 155 mg.; blood sugar, 0.19 per cent. Eye-grounds negative. Death, Oct. 23, 1919. Necropsy: No edema; no ascites; hydrothorax (300 c.c.). Heart enlarged. Kidneys weighed 300 gm.; finely granular surfaces. Some of the glomeruli are completely sclerosed but the great majority show the hyaline change just beginning. There are enormous numbers of disintegrated polymorphonuclears in the interstitial tissues and in the damaged glomeruli (Fig. 16). There is advanced atrophy of most of the tubules and moderate atrophy of the others.

Case 44 (A-10-145).—Male, aged 32 years. Duration unknown. Urine: abundant albumin, hyalin and granular casts. No other clinical data. Necropsy: Ascites, hydrothorax, hydropericardium, edema of the lungs. Heart weighed 530 gm.; kidneys, 314 gm. Nearly all the glomeruli are of about the same appearance. They are enlarged, their capillaries are practically all closed by swollen endothelium, but none of them has yet become hyaline. Occasional remnants of polymorphonuclears are seen in glomeruli and tubules. There is very marked tubular atrophy.

Case 45 (A-11-77).—Male, aged 70 years; admitted to hospital June 7, 1911. Complained of edema and shortness of breath. Urine: albumin, hyalin and granular casts. Specific gravity, from 1.018 to 1.024. Death, July 18, 1911. Necropsy: General anasarca, ascites, hydrothorax and hydropericardium. Heart weighed 475 gm.; old mural thrombus in left auricle. Kidneys weighed 335 gm.; smooth external surfaces. There are a few hyalin glomeruli; but the great majority are not so far advanced. There is complete closure of all but a very few capillaries in each glomerulus. Occasional nuclear fragments are seen in the glomeruli which may be remnants of polymorphonuclears. There are many partially disintegrated polymorphonuclears in the tubules. There are a large number of old epithelial crescents. Tubular atrophy is very marked.

There is very little clinical history available in Cases 46 and 47, but the microscopic structure suggests cases of long duration with a fairly recent inflammation in the persistent glomeruli.

Case 46 (A-12-40).—Male, aged 33 years. Duration of illness unknown. Was comatose and breath had a uremic odor. Edema of face. Systolic blood pressure, from 200 to 210. Diarrhea. No marked changes in eye-grounds. Moderate amount of albumin and numerous casts. Necropsy: Slight edema of face and neck. A little fluid in the serous cavities. Heart weighed 735 gm.; kidneys, 250 gm.; granular surfaces. A large percentage of the glomeruli are hyaline. Other glomeruli are enlarged and show closure of most of the capillaries. Numerous well preserved polymorphonuclears are visible in the open and closed capillaries, suggesting a recent acute attack.

Case 47 (0-12-83).—Female, aged 17 years. For several years the patient had symptoms which were referred to the urinary tract. No details of the clinical picture were recorded. A diagnosis of renal tuberculosis was made and one kidney was removed Nov. 18, 1912. Subsequent history unknown. The kidney shows a finely granular surface. A large number of glomeruli are hyaline; the others are enlarged and show a great increase of nuclei with closure of most of their capillaries. Large numbers of disintegrating polymorphonuclears are to be seen in the closed capillaries (Figs. 12, 13 and 14). The tubules belonging to the hyaline glomeruli have completely disappeared; the others show varying degrees of atrophy.

Cases 48 to 51 give histories which may be interpreted as examples of chronic nephritis following acute nephritis, and in Cases 49 and 51 there is good evidence of a terminal acute exacerbation.

Case 48 (A-15-363).—Male, aged 30 years, has had frequent urination for past five or six years. Three years ago he suddenly developed general edema. Was in the hospital three weeks at this time. Left hospital much improved. Has had attacks of edema and shortness of breath since then. Edema is worse after alcoholic excesses. Has been confined to his home since about Sept. 10, 1915. Admitted to hospital Oct. 10, 1915, with a severe attack similar to the one he had three years ago. Phenolsulphonephthalein, October 16, a trace. Urine: specific gravity, from 1.010 to 1.014; abundant albumin; many casts. Leukocytes, 7,400. Death, Nov. 14, 1915. Necropsy: Marked edema of lower half of body, ascites, hydrothorax and hydropericardium. Heart weighed 575 gm.; kidneys, 155 gm.; granular surfaces. A large majority of the glomeruli are hyaline and their associated tubules show extreme atrophy; the others are damaged in varying degrees, due to closure of part of their capillaries. Many of the tubules associated with these injured glomeruli show very little atrophy.

Case 49 (A-17-62).—Female, aged 27 years. Mother died of Bright's disease at 49. One brother has kidney trouble now. Patient had otitis media in 1906, and smallpox in 1908. In October, 1909, she developed severe headaches, high fever, edema of ankles and ascites. Blood pressure during this attack, 160 systolic. She was in bed from October, 1909, to April, 1910. There was gradual improvement but she had recurring attacks of headache, edema of ankles and vomiting. Had a mastoid infection in 1915. Scarlet fever in the fall of 1916. Polyuria the past three years. Eyesight always poor. In October, 1916, she had a sore throat with high fever and the edema became worse. Vision has gradually grown poorer. Has been in bed since Feb. 24, 1917. Admitted to hospital March 1, 1917. Urine: specific gravity, from 1.005 to 1.008; large quantities of albumin, many leukocytes, a few granular casts. Hemoglobin, 40 per cent.; erythrocytes, 2,300,000; leukocytes, 11,000 (March 3); 22,400 (March 13)—92 per cent. polymorphonuclears. Blood pressure, March 1, 185/100. Temperature about normal. Blood chemistry: creatinin, March 1, 26 mg.; March 16, 22.2 mg. Urea nitrogen, March 1, 101.2 mg.; March 16, 68 mg. Phenolsulphonephthalein, 0 per cent. March 2 and March 10. Death, March 17, 1917. Necropsy: Marked edema of face, ascites, hydrothorax and hydropericardium. Heart weighed 455 gm.; kidneys, 150 gm.; rough granular surfaces. A large majority of the glomeruli are completely sclerosed and their tubules have almost disappeared; the others are enlarged and show closure of most of their capillaries, and partial atrophy of their associated tubules. In this latter group of glomeruli there are many polymorphonuclear leukocytes in both the open and closed capillaries. These histologic features suggest an acute exacerbation of a chronic nephritis. There are a few old extracapillary lesions.

Case 50 (A-18-117).—Male, aged 32 years. No history of scarlet fever or rheumatism. Ten years ago he was in a hospital with a condition diagnosed Bright's disease by his physician. He remembers that he had a considerable amount of edema at that time. His present illness began about the end of March, 1918, with weakness, loss of appetite, vomiting after eating and unproductive cough. Admitted to hospital May 21, 1918. Patient thinks he has lost about 20 pounds during the last two months. Physical Examination: Enlarged heart, systolic murmur at apex, dyspnea, slight edema of lungs. Blood pressure, 190/140. Daily urine excretion from 175 to 225 c.c. Moderate albuminuria, casts; many erythrocytes. Phenolsulphonephthalein, 0 per cent. on two occasions. Urea nitrogen, from 15.5 to 17 mg.; creatinin, from 2 to 3.6 mg. Blood sugar, from 0.092 to 0.11 per cent. Death, June 3, 1918. Necropsy: No edema; ascites (100

c.c.); hydrothorax (1,300 c.c.). Fibrinous pericarditis. Heart weighed 630 gm.; spleen, 240 gm.; kidneys, 405 gm.; granular surfaces. About one half of the glomeruli are completely sclerosed, and their tubules have almost disappeared. The others are enlarged and show closure of most of their capillaries but no definite hyaline changes. Their tubules are notably decreased in size. A number of these glomeruli show hyaline degeneration of the afferent arteriole. Remnants of polymorphonuclears are visible in most of the enlarged glomeruli and throughout the interstitial tissues. There are many epithelial crescents. It is probable that the sclerosed glomeruli are due to the attack ten years ago.

Case 51 (A-19-264).—Male, aged 29 years, had scarlet fever at 23. Was unable to work for six months following this disease (no information as to edema or albuminuria). Had an attack of rheumatism at 27 which lasted six months. At 28 he had arthritis in the ankles and wrists, relieved by tonsillectomy in the spring of 1919. In October, 1919, he contracted a severe cold from exposure in a cold rain. The next day he was in bed with severe headache, palpitation, dyspnea, precordial pain, edema around the eyes, epistaxis and blurring of vision. He has grown worse gradually since that time. Admitted to hospital, Nov. 6, 1919. Examination showed enlargement of heart with a systolic murmur, puffiness of face and conjunctival hemorrhages. Blood pressure, 170/80. During his stay in the hospital he had frequent attacks of vomiting, nosebleed, hiccough, headache and dizziness. Became unconscious December 8. Hemoglobin, from 32 to 25 per cent. Erythrocytes from 2,650,000 to 1,800,000. No fever. Urine: large amount of albumin, hyalin and granular casts, a few erythrocytes. Phenolsulphonephthalein, November 14, a trace; November 21, 5 per cent. Blood chemistry: November 9, creatinin, 7.4 mg.; urea nitrogen, 87 mg.; blood sugar, 0.153 per cent.; November 20, creatinin, 10.8 mg.; urea nitrogen, 36 mg.; blood sugar, 0.189 per cent. Alkaline reserve, November 20, 40.6. Death, Dec. 8, 1919.

Necropsy: Slight edema of face; hydropericardium (100 c.c.). Heart weighed 435 gm.; vegetations on wall of left auricle. Spleen weighed 365 gm.; kidneys, 340 gm.; finely granular surfaces. A number of glomeruli show complete sclerosis with disappearance of their tubules. A large number show old extracapillary lesions without hyalinization of the tuft but with well advanced atrophy of their tubules. More than one third show an appearance corresponding with the subacute stage, i. e., great enlargement due to swelling and proliferation of the endothelium, with many polymorphonuclears in the closed capillary loops. The tubules belonging to this latter group show moderate to well advanced atrophy. There are masses of polymorphonuclears in some of the tubules. There are large areas of cortical tissue densely infiltrated with mononuclear leukocytes—an appearance characteristic of the acute interstitial nephritis of scarlet fever (Fig. 18). The appearances suggest an old nephritis dating from the attack of scarlet fever, and an acute attack of rather recent date.

Case 52 is a good illustration of terminal acute glomerulitis in a case of very long duration.

Case 52 (A-17-207).—Female, aged 46 years, has had a discharge from the left ear as long as she can remember. Frequent attacks of sore throat and pleurisy. Operation for myoma of uterus when 27 years old. Present trouble began in 1900 with nocturia and gastric disturbances. Some improvement on a milk diet. Was refused life insurance in 1906 because of albuminuria. Was under treatment for this condition from time to time but did not improve. In bed, on a milk diet, for eight days in August, 1915. Admitted to hospital, May, 1917. Poor vision. Cramps in muscles. Urine: trace of albumin; casts very rare. Hemoglobin, 49 per cent.; leukocytes, 11,000. Phenolsulphonephthalein, a trace. Blood pressure, 117/80. Urea nitrogen, from 39 to 66 mg.;

creatinin, from 9.7 to 16.8 mg.; blood sugar, from 0.16 to 0.2 per cent. Discharged June 23. Readmitted, Sept. 29, 1917. Headache, nausea, vomiting, dyspnea, swelling of face and legs, loss of appetite, cramplike pains in fingers and frequent urination. Eleven hundred c.c. of fluid was drawn from right pleural cavity. October 3, urine: moderate amount of albumin, occasional hyalin casts. Hemoglobin, 25 per cent.; erythrocytes, 3,000,000; leukocytes, 7,600. Blood pressure, 160/110. Phenolsulphonephthalein, a trace. Urea nitrogen, 89 mg.; creatinin 16.2 mg. Temperature normal. Death, Oct. 6, 1917. Necropsy: general anasarca; ascites (1,500 c.c.); hydrothorax (800 c.c.). Heart weighed 400 gm.; spleen, 120 gm. Pus in left middle ear. Slight general arteriosclerosis. Kidneys, weighed 120 gm.; rough, granular surfaces. A large percentage of the glomeruli are completely sclerosed; the others show an acute or subacute glomerulitis. These latter are enlarged with greatly swollen endothelium, which closes most of the capillaries. The numerous polymorphonuclears in the capillaries and tubules as well as fresh epithelial crescents indicate that there has been a recent acute attack.

Cases 53 to 59 are clinically examples of the type with slow insidious onset and long duration. Microscopically they show very old lesions without any acute processes.

Case 53 (A-11-76).—Female, aged 44 years. Admitted to hospital Aug. 9, 1910. Complained of edema which had been present at varying intervals since her first pregnancy nearly fifteen years before. Had scarlet fever when a child. Has had headaches and vomiting spells for many years. Shortness of breath and swelling of feet for the past three years. Albumin and casts continuously present in the urine. Hemoglobin, from 50 to 60 per cent. Systolic blood pressure, 140 to 170. Extreme edema. Eighty-one gallons of fluid was drawn from the pleural and peritoneal cavities during her stay in the hospital. Multiple abscesses of the skin of the arms and legs appeared a few months before death. Streptococci were found in these abscesses. Low fever during most of her stay in the hospital. Death, July 17, 1911. Necropsy: Anasarca, ascites, hydrothorax and hydropericardium. Heart weighed 492 gm. Fresh mural thrombus in left ventricle. Kidneys weighed 260 gm. Granular surfaces. About one-third of the glomeruli are completely hyalinized and their tubules have largely disappeared. Most of the other glomeruli are associated with markedly atrophic tubules and show closure of nearly all the capillaries with beginning hyaline degeneration (Fig. 19). A few glomeruli show a number of permeable capillaries, and these glomeruli belong to tubules of normal size. Renal function was performed by a number of damaged glomeruli.

Case 54 (A-13-178).—Female, aged 32 years. Many attacks of tonsillitis when young; none recently. Present illness began about one year ago with shortness of breath on slight exertion. In June, 1913, she first noticed swelling of legs which would disappear after a night's rest. Was in bed sixteen weeks before admission to hospital. On admission, Nov. 21, 1913, there was general subcutaneous edema, enlargement of heart, and hypertrophied tonsils. Urine: abundant albumin, many hyalin granular casts. Leukocytes, November 22, 13,700; 80 per cent. polymorphonuclears. Blood pressure, November 24, 160/110; December 8, 110/100. Death, Dec. 9, 1913. Necropsy: General anasarca, hydrothorax, hydropericardium, ascites and edema of lungs. Heart weighed 543 gm. Double pyosalpinx. Streptococcus from heart's blood. Kidneys weighed 190 gm. Granular surfaces. Large majority of glomeruli sclerosed. Other glomeruli show partial closure of their capillaries with a corresponding atrophy of the associated tubules.

Case 55 (A-13-184).—Female, aged 34 years. Duration of illness about 10 months. Hemoglobin 30 per cent. No clinical history available. One

kidney removed at necropsy; granular surface. Many sclerosed glomeruli. No normal glomeruli are found. The great majority show severe injury and are connected with markedly atrophic tubules. These injured glomeruli are enlarged and nearly all their capillaries are closed (Fig. 9). There are a number of polymorphonuclear remnants in the closed capillaries. A number of old epithelial crescents are seen.

Case 56 (A-17-108).—Male, aged 39 years. Has had scarlet fever, date unknown. Present illness began three years ago with swelling of ankles. Later his legs and face began to swell. Still later he developed dyspnea and palpitation of the heart. Admitted to hospital, April 18, 1917. Had edema of ankles, headache, poor vision. Urine: specific gravity, 1.014; albumin, trace to a large amount. Leukocytes, 11,800. Phenolsulphonephthalein, 0 per cent, May 2. Death, May 18, 1917. Necropsy: No edema; no ascites; hydrothorax (600 c.c.); hydropericardium (200 c.c.). Heart weighed 640 gm.; kidneys, 350 gm.; surfaces roughened and pitted. Large numbers of hyalin glomeruli are seen; the other glomeruli are all enlarged, most of their capillaries are closed and there are varying degrees of hyaline degeneration in the lobules (Figs. 15 and 20). Numerous degenerated polymorphonuclears are seen in the closed capillaries and in atrophic tubules. There are a few rather recent epithelial crescents. An occasional afferent glomerular artery shows hyaline degeneration.

Case 57 (A-17-118).—Male, aged 69 years. One brother died of Bright's disease. Patient first noticed swelling of his feet, especially at night, thirteen years ago. For the last few years he has noticed puffiness under the eyes. He has been in a hospital on two previous occasions for the same condition that troubles him now. Admitted to hospital, April 18, 1917. Has severe dyspnea. Left leg is greatly swollen. Blood pressure, April 27, 185/140. Urine: trace of albumin, many casts; specific gravity from 1.012 to 1.022. Leukocytes, 9,600. Phenolsulphonephthalein, April 27, 12 per cent. Blood chemistry, April 27: creatinin, 1.5 mg.; urea nitrogen, 28 mg. Alkaline reserve, 46. Death, June 8, 1917. Necropsy: Marked edema of lower extremities; left hydrothorax (100 c.c.); edema of lungs. Heart weighed 495 gm.; extensive sclerosis of aorta and large vessels. Kidneys weighed 160 gm.; rough granular surfaces. A large number of glomeruli are completely sclerosed; many others are enlarged with closure of most of their capillaries. There are a number of old extracapiliary lesions. Many of the afferent glomerular arteries show hyaline degeneration, and the obliteration of some of the glomeruli is evidently due to this cause.

Case 58 (A-18-94).—Male, aged 50 years. Never had scarlet fever, rheumatism or tonsillitis. Well until his present illness began six or seven years ago, when he first noticed swelling above the tops of his shoes, especially in the evening. This condition grew worse and at times there was also swelling of the hands. For the past five years he had noticed weakness and dyspnea, most pronounced during the past few weeks. Admitted to hospital, April 7, 1918. Physical Examination: Loss of weight; enlargement of heart to the left; systolic murmur at aortic area and at apex. Urine: specific gravity from 1.006 to 1.015; trace to a heavy precipitate of albumin; numerous granular casts. Low fever. Hemoglobin, 75 per cent. Erythrocytes, 4,420,000; leukocytes, 7,800. Blood pressure, April 11, 188/124. Death, May 3. Necropsy: Edema of face; no fluid in serous cavities. Heart weighed 640 gm.; kidneys, 205 gm.; finely granular surfaces. A large majority of the glomeruli are completely sclerosed; the others are enlarged and show closure of most of their capillaries.

Case 59 (A-19-2).—Male, aged 25 years. No history of scarlet fever, tonsillitis or rheumatism. In good health until April 1, 1918, when he began to have attacks of headache and vomiting. The attacks would last a day, after which he would be able to work again. Has had a few attacks of precordial pain, one of which lasted eight hours. Shortness of breath was first noticed about the

middle of November, 1918. He has been in hospitals on four different occasions since April 1, 1918. Admitted to University Hospital Dec. 14, 1918. No edema. Mitral regurgitation. Blood pressure, December 15, 210/118. Urine: large amount of albumin; many granular casts; specific gravity, 1.010. Leukoctyes, December 19, 10,500. Low fever. Blood chemistry: December 27, urea nitrogen, 57.3 mg.; creatinin, 12 mg.; January 4, urea nitrogen, 72 mg.; creatinin, 12.4 mg. Phenolsulphonephthalein, December 20, a trace. Albuminuric retinitis. Death, Jan. 5, 1919. Necropsy: No edema; ascites (150 c.c.); hydrothorax (400 c.c.); early bronchopneumonia. Heart weighed 500 gm.; kidneys, 195 gm.; rough granular surfaces. Over three fourths of the glomeruli are completely sclerosed and their tubules have almost disappeared. The remaining glomeruli are badly damaged, only a small part of their capillaries being permeable. Their tubules are moderately atrophic. An occasional old extracapillary lesion is seen. There are no polymorphonuclears in the glomeruli.

Cases 60 to 68 are cases with short clinical histories but with gross and microscopic evidence of very long duration.

Case 60 (A-13-145).—Male, aged 35 years, has had diphtheria and scarlet fever. Present illness began three months before admission with dyspnea and swelling of feet. Admitted to hospital Sept. 10, 1913. Chief complaints were gastric distress and edema. Heart was enlarged. Urine: specific gravity, 1.010; abundant albumin; hyalin, granular, waxy and leuckocyte casts. Systolic blood pressure, September 27, 132. Died in coma, Sept. 29, 1913. Necropsy: Ascites and hydrothorax. Heart weighed 475 gm.; kidneys, 169 gm.; surfaces very granular. Apparently about two thirds of the glomeruli are hyalinized and their tubules have disappeared. The remaining glomeruli are enlarged, and a large percentage of their capillaries are occluded (Fig. 21). In some of these, there are remnants of polymorphonuclears in the closed capillaries. The tubules connecting with these defective glomeruli are moderately atrophic. There are large areas of lymphocytes in the cortex, probably representing an interstitial exudate which occurred during the attack of scarlet fever. This suggests that the glomerular involvement may date from the attack of scarlet fever.

Case 61 (A-14-192).—Male, aged 30 years. Admission, Sept. 28, 1914. No clinical history. Urine: specific gravity from 1.008 to 1.018; abundant albumin, many casts. Blood pressure, October 7, 192 systolic. Death, Oct. 13, 1914. Necropsy: Slight edema of extremities; ascites. Heart weighed 490 gm.; kidneys, 360 gm.; granular surfaces. A small proportion of the glomeruli are completely sclerosed; the majority show extensive obliteration of their capillaries with marked atrophy of their tubules. A few glomeruli are normal. Rarely an old extracapillary lesion is seen. A great many disintegrating polymorphonuclears are found in the atrophic tubules.

Case 62 (A-15-373).—Male, aged 23 years, admitted to hospital Sept. 26, 1915, has had frequent attacks of sore throat and rheumatism (?). About one month before admission he noticed slight swelling of his feet, and gradually increasing weakness and shortness of breath. Kept at work until about Sept. 12, 1915. On admission he complained of weakness, dizziness, headache, cough and nocturia. Urine (nine examinations): specific gravity, from 1.010 to 1.012; albumin, trace to a heavy precipitate; many casts. Blood pressure, October 13, 180/115. Phenolsulphonephthalein, October 1, 11 per cent. Leukocytes, November 15, 5,800. Death, Nov. 23, 1915. Necropsy: No edema; no fluid in serous cavities. Heart weighed 557 gm. Kidneys small with granular surfaces. A large percentage of the glomeruli are completely hyalinized, and the others show partial closure of their capillaries.

Case 63 (A-15-394).—Male, aged 54 years, admitted to hospital, Oct. 19, 1915. Seven years ago he had an attack of acute arthritis (ankles were swollen,

red and painful). Nine days before admission he began to have dyspnea and five days later his legs began to swell. Abdomen has been distended since about October 5. On admission he had marked edema of lower extremities and external genitals, and enlargement of the heart with mitral regurgitation. Urine (sixteen examinations): albumin, trace to a heavy precipitate; casts. Blood pressure, October 19, 150/90; November 4, 168/90; December 6, 100/58. Death, Dec. 7, 1915. Necropsy: No edema; hydropericardium. Heart weighed 650 gm. Mitral leaflets greatly thickened and retracted; aortic leaflets adherent. Lobar pneumonia. Advanced sclerosis of aorta. Kidneys weighed 319 gm.; roughened granular surfaces. A large percentage of the glomeruli are completely sclerosed; the others show partial closure of their capillaries. There is advanced sclerosis of some of the larger arteries and a few of the afferent arterioles. The fact that most of the afferent arterioles are not diseased indicates that the vascular disease is not the main cause of the glomerular changes.

Case 64 (A-16-132).—Male, aged 27 years. About three months before admission he began to have attacks of nosebleed. These recurred frequently and have gradually become more severe. About seven weeks before admission his left wrist pained him severely. Entered hopsital, March 26, 1916, complaining of frequent epistaxis, pain in stomach with occasional vomiting, sore throat and general weakness. Small hemorrhages were noted on the left wrist and on the palate. There was edema of the uvula and pharynx, and a mitral systolic murmur. Temperature, from 100 to 101 F. Hemoglobin, 36 per cent.; erythrocytes, 2,800,000; leukocytes, 9,200; 87 per cent. polymorphonuclears. Urine: large amount of albumin; some blood. Death, March 30, 1916. Necropsy: No edema; ascites (50 c.c.); hydrothorax (100 c.c.). Aorta, normal. Heart weighed 425 gm.; kidneys, 150 gm.; roughened granular surfaces. More than three fourths of the glomeruli are completely sclerosed, and the others show many closed capillaries. Occasional partially atrophied tubules shows masses of disintegrating polymorphonuclears. A few afferent arterioles show hyaline degeneration.

Case 65 (A-16-384).—Male, aged 24 years. One brother died of Bright's disease at 23. Patient stated that he had been perfectly well until August, 1916, when he had an attack of nosebleed. At first the attacks came about once a week, and would last one to two hours, but later, they became more frequent. He gradually became weaker. Did not notice swelling of feet or puffiness of eyes until about November 5. Admitted to hospital, Nov. 12, 1916. Urine: specific gravity, 1.010; large amount of albumin; many casts of all kinds. Hemoglobin, 20 per cent.; erythrocytes, 1,500,000; leukocytes, 7,500. Blood pressure, 170/90. Phenolsulphonephthalein, November 12, 0 per cent. Blood chemistry, November 13: creatinin, 27.2 mg.; urea nitrogen, 131 mg.; sugar, 0.26 per cent.; alkaline reserve, 18.3. Death, November 18, 1916. Necropsy: No edema; no ascites; hydrothorax (200 c.c.). Heart weighed 415 gm. Aorta normal. Kidneys weighed 205 gm.; roughened granular surfaces. Practically all the glomeruli are severely involved. There is advanced atrophy of all the tubules. Many atrophic tubules contain masses of disintegrating polymorphonuclears. There are some old extracapillary lesions.

Case 66 (A-19-160).—Male, aged 32 years. Recently discharged from the army because of heart and kidney trouble. No details of history available. Admitted to hospital July 26, 1919. Normal temperature. Frequent vomiting. Became irrational July 27. Blood pressure, 120/80. Systolic murmur at apex. Dilated heart. Urine: large amount of albumin; no casts; no erythrocytes. Death, July 30, 1919. Necropsy: No edema; no fluid in serous cavities. Heart weighed 350 gm.; dilated. Kidneys weighed 140 gm.; finely granular surfaces; thinned cortices. A large majority of the glomeruli are completely sclerosed, and most of the others are severely damaged and their tubules are markedly atrophic. An occasional glomerulus is practically normal. There are a large number of old extracapillary lesions.

CASE 67 (A-18-180).—Male, aged 26 years, admitted to hospital, Sept. 17, 1918. Death, Sept. 18, 1918. No history was obtained. Urine: specific gravity, 1.015; small amount of albumin; many granular casts. Necropsy: Edema of ankles; marked ascites, hydrothorax and hydropericardium. Heart weighed 360 gm.; spleen, 235 gm.; kidneys, 290 gm.; external surfaces smooth. About one-third of the glomeruli are completely sclerosed and their tubules are very small. The other glomeruli are moderately enlarged, most of their capillaries are closed and their tubules are moderately reduced in size. There are numerous disintegrated polymorphonuclears in the closed capillaries and some of the tubules. Many glomeruli show a thick band of hyaline around the afferent artery after its entrance into the glomerulus; but there is very little change in the artery before it reaches the glomerulus.

CASE 68 (A-20-204).—Male, aged 34 years. Typhoid fever at age of 17 years; was in bed 10 weeks. In March, 1920, he first noticed impairment of vision. At this time he had frequent headaches with a catarrhal condition in the upper respiratory tract. His physician told him that he had nephritis. May 4, 1920, examination revealed enlargement of heart, albuminuric retinitis, and a blood pressure of 200/120. Death, May 20, 1920. Necropsy: Slight edema of face; ascites (100 c.c.); hydrothorax (2,200 c.c.); edema of lungs. Heart weighed 425 gm.; kidneys, 195 gm.; granular surfaces. Many sclerosed glomeruli with disappearance of their tubules. Majority of glomeruli are enlarged and their capillaries are largely occluded by swollen endothelium but there is very little hyaline degeneration. There is a notable proliferation of the capsular epithelium. The tubules show advanced atrophy.

CASE 69 (A-17-230).—Male, aged 45 years. Well until the autumn of 1916 when he developed swelling of the feet and abdomen with marked weakness. Improved under hospital treatment but was too weak to return to work. In the summer of 1917 he had another similar attack. There was marked general edema and a systolic murmur at the apex of the heart. Admitted to hospital Sept. 29, 1917. Blood pressure, October 1, 140/70; October 20, 130/80. Urine, September 29 to November 6; abundant albumin, many casts of all types. Leukocytes, October 15, 8,700. Phenolsulphonephthalein, October 1, 35 per cent.; October 15, 31 per cent. Blood chemistry, October 2: urea nitrogen, 24.2 mg.; creatinin, 2.3 mg. November 1, left side of face became swollen and six teeth were extracted. Lobar pneumonia was recognized November 9. Leukocytes 26,000 on November 9. Death, Nov. 11, 1917. Necropsy: No edema; no fluid in serous cavities. Extensive old pleuritic adhesions. Lobar pneumonia. Heart weighed 400 gm.; spleen, 120 gm.; kidneys, 360 gm.; adherent capsules; slightly roughened external surfaces; grayish yellow cortices. Very few glomeruli are hyaline. The great majority of the corpuscles show old epithelial crescents surrounding small partially collapsed glomeruli with few or no permeable capillaries. The tubules connected with these glomeruli are markedly atrophic but still easily visible (Fig. 22). There are a number of glomeruli, however, that have many permeable capillaries and are connected with fairly normal tubules. These presumably explain the fairly good renal function.

Age.—The age of the subacute and chronic cases at the time of death is shown by decades in Table 2. It will be noted that two-thirds of the cases occurred in the third and fourth decades. Fitz [31] at the Massachusetts General Hospital, found an average age of 32 years in cases of chronic glomerulonephritis, and 52 years in the arterio-

31. Fitz, R.: The Phenolsulphonephthalein Test and the Nonprotein Nitrogen of the Blood in Chronic Nephritis, Boston M. & S. J. **183**:247, 1920.

sclerotic form of Bright's disease. Two-thirds of our cases of arteriosclerotic renal disease were over 50 years old.

TABLE 2.—Age at Death

Age	Number of Cases
0-10 years	1
11-20 years	1
21-30 years	12
31-40 years	12
51-50 years	5
51-60 years	4
61-70 years	2

Sex.—There were twenty-seven males and nine females, but the proportion of males to females in our necropsies is approximately 2:1 (2,325 males and 1,063 females in 3,388 necropsies) so that there is probably only a slight preponderance of the disease in males.

Duration.—The duration of the subacute cases was usually less than four months; but one patient (Case 36) lived six months, and another (Case 40) had an abnormal urine one year before death.

The actual duration of a chronic case cannot be determined entirely by the patient's statement as to when his illness began. Seven well defined chronic cases with contracted kidneys gave histories of an illness of only two or three months' duration. Probably the disease could have been recognized long before in these patients, but it evidently did not produce serious discomfort until well advanced.

Twelve patients had symptoms of nephritis for one year or more before death, and in seven of these the disease was present over three years. Case 49 lasted eight years and Case 52 over eleven years.

Symptoms.—The disease usually develops slowly, but sometimes the onset is rapid, even in cases in which extensive destruction of renal tissue must have been present long before the appearance of symptoms. The most frequent initial complaints are dyspnea and edema; but in occasional cases epistaxis or gastrointestinal disturbances, such an anorexia, vomiting and gastric distress may bring the patient to his physician. Other symptoms which may be prominent at some time during the course of the disease are headache, weakness, precordial pain, frequent urination and disturbances of vision.

Edema.—This is a very common sign of nephritis. Subcutaneous edema was present in thirty-one of thirty-six cases in which data were available; and even in the five dry cases there was a little fluid found in the serous cavities at necropsy. The intensity of the edema varies greatly in different patients and in the same patient from time to time. It is influenced by rest, the amount of salt in the diet and other unknown factors. It may disappear before death. The accumulation of fluid in the serous cavities is sometimes a prominent and serious

feature of the disease. Eighty-one gallons of fluid were drained from the pleural and peritoneal cavities of one patient (Case 53) during a period of eleven months. Hydrothorax and edema of the lungs are partly responsible for dyspnea, which is a very frequent symptom.

Hypertension and Cardiac Hypertrophy.—These are almost constantly present in chronic glomerulonephritis. Blood pressure was recorded in twenty of the chronic cases, and in only two instances was the systolic reading below 140. These low pressures were both taken shortly before death and may not be exceptional since it frequently happens that the pressure falls a short time before exitus. The systolic pressure was from 160 to 180 in six patients, and 180 or above in ten.

The average weight of the heart in twenty-six chronic cases was 498 gm. Only three hearts weighed less than 400 gm. One of these (Case 42) was a case of comparatively short duration, judged both by the clinical history and the structural changes in the kidneys. In the other two cases (Cases 66 and 67) no clinical history was available, but the histologic picture indicated a disease of long duration, so that these seem to be examples of chronic glomerulonephritis without cardiac hypertrophy. There is no notable enlargement of the heart in the subacute cases, but hypertension was found in the three cases in which the blood pressure was taken.

Anemia.—This is apparently a frequent complication in advanced chronic glomerulonephritis and it seems to increase in intensity toward the end of the illness. The hemoglobin was determined in ten chronic cases, and found to be below 50 per cent. in eight of them. One patient (Case 58) had a hemoglobin of 75 per cent. one month before death.

Urinary Changes.—Urinary examinations are recorded in thirty-four of the thirty-seven cases of this group. Albumin was found in every sample of urine from every patient. Usually a large amount was found but occasionally only a trace was present. When a large number of examinations are made on the urine of one patient the amount of albumin may vary from a trace in some samples to a heavy precipitate in others. We have no cases of glomerulonephritis with normal urine. Casts were found in thirty of thirty-four cases, and usually in large numbers. In the cases in which no casts were found only one sample of urine was examined. Casts may be rare in one sample and numerous in another sample of urine from the same patient. Bloody urine was recorded in one chronic and three subacute cases. Of course, only a small percentage of persons who have albumin and casts in the urine are suffering from Bright's disease. Brown [32] in a study

32. Brown, P. K.: A Study of the Etiology of Chornic Nephritis, J. A. M. A. **66**:793 (March 11) 1916.

of 7,000 hospital admissions found 594 with albumin and casts, of which only thirty-eight (6.4 per cent.) were considered to have Bright's disease.

Functional Tests.—Functional studies were made on sixteen patients. The tests were applied five months before death in two patients, and within the last two months of life in all the others. The phenolsulphonephthalein output was invariably greatly reduced, and in eleven patients in which it was determined shortly before death it varied from 0 to 20 per cent. In Case 69 the readings were higher but this patient died of lobar pneumonia before serious renal insufficiency had developed.

Marked retention of urea nitrogen and creatinin was usually observed. The exceptions are Case 36, in which the test was made very early in the attack, and Case 50, which is inconsistent with the phthalein excretion and probably an error. In Case 69, in which death was due to lobar pneumonia there was only slight retention. As is well known urea nitrogen begins to increase before there is any change in the amount of creatinin.

These tests usually run parallel and are of about equal value in estimating renal sufficiency. It is desirable to use both tests since each acts as a control on the other and both are entirely consistent with the structural changes found at necropsy. We have not seen any cases of marked inconsistency between these functional tests and the findings at necropsy. Functional tests are of no great value in acute glomerulonephritis since in these kidneys the damage is usually not permanent; but in chronic nephritis they give a fairly accurate measurement of the extent of the permanent injury. The difficulty with these tests is that they do not reveal the presence of nephritis until two-thirds or more of the renal filter has been closed, and they are therefore of no value in the recognition of the early stages of the disease when there might be some chance for successful therapy.

Functional tests are frequently useful in distinguishing a case of primary hypertension from one of chronic Bright's disease, and also in determining the extent of the renal injury in the arteriosclerotic kidney; but it is not often possible to distinguish this last named renal disease from chronic glomerulonephritis by functional tests. Occasionally patients may live a long time with a high degree of retention of metabolites in the blood and a very low phthalein excretion (O'Hare [33]), but, as a rule, such findings indicate that death will occur within a few months at most. In making a prognosis it is to be remembered that in acute nephritis and in acute exacerbations of a chronic

33. O'Hare, J. P.: Compatibility of Long Life with Low Renal Function, J. A. M. A. **73**:248 (July 26) 1919.

nephritis there is a temporary obstruction of many capillaries which open up again as the acute process subsides. Tests made during these acute stages indicate a more extensive destruction of renal tissue than actually exists.

Our data are not complete enough to warrant a statement as to the frequency of albuminuric retinitis.

Death in subacute and chronic glomerulonephritis seems to occur almost invariably as a direct result of renal insufficiency. A severe anemia is usually present in the terminal stages. Cardiac decompensation seems never to be the direct cause of death. Occasionally a seropurulent pleuritis or a bronchopneumonia of limited extent is found at necropsy. In only one case was death definitely due to a complication, viz., lobar pneumonia in Case 69.

Gross Changes in the Kidneys.—In subacute glomerulonephritis the kidneys may be of normal size but are usually enlarged. They are never contracted. In five out of eight adults the kidneys weighed more than 400 gm. In one instance the weight was 500 gm. and in another 630 gm. The external surfaces are smooth. The cortices are cloudy.

In the twenty-five chronic cases in which the weights are recorded the average was 248 gm. In ten cases the kidneys weighed less than 200 gm., in eight cases more than 300 gm., and in three cases more than 350 gm. The maximum weight was 405 gm. In a general way there is a relation between the duration of the disease and the size of the kidneys, the smaller kidneys being found in cases with histories of a long illness; but there are many exceptions. The external surfaces are almost invariably roughened and granular, a condition produced by an uneven atrophy of the cortex. The cortex is cloudy, reduced in thickness, and indistinctly marked off from the pyramids. Multiple small superficial cysts and adenomas do not seem to occur in uncomplicated glomerulonephritis but these structures are very common in arteriosclerotic kidneys.

Microscopic Appearances.—In chronic cases there are always a large number of hyalin glomeruli. These are smaller than normal and are of homogeneous structure. Their tubules may appear as small solid cords of cells, or they may have disappeared entirely. Roughly estimated, the number of hyalin glomeruli varies from one-third in some cases to three-fourths in others. These tubule systems are of course nonfunctional. The other glomeruli are practically all injured in varying degrees. Very few are entirely normal. The most important change is the permanent closure of various parts of the capillary network. Some glomeruli show closed portions here and there while others may show only an occasional permeable capillary

(Fig. 23). The size of the associated tubule depends on the permeability of its glomerulus. The tubular atrophy is pronounced when the capillaries are mainly closed. The work of the kidney is performed by damaged glomeruli (Figs. 17, 19, 23).

In the subacute kidneys the changes are not so far advanced. The glomeruli show closure of the capillaries by swollen endothelium with beginning hyaline degeneration, but very few glomeruli have become completely hyalinized. The subacute case differs from the chronic in the more uniform injury of all the glomeruli. Death in the subacute case occurs before any glomeruli have had time to reach the hyaline stage. In the chronic case the severely injured glomeruli become hyalin, while those less injured carry on the renal function.

The evidences of previous acute processes in chronic kidneys will be discussed later on.

ETIOLOGY OF SUBACUTE AND CHRONIC GLOMERULONEPHRITIS

The clinical and pathologic evidence that acute glomerulonephritis is due to bacterial infection is so convincing that this view has very few opponents at present; but there are many who do not believe that infection is the basis of the chronic form, and either attribute it to obscure metabolic disturbances or consider the etiology entirely unknown. The evidence as to the etiology of subacute and chronic glomerulonephritis will now be discussed.

1. *The Relation Between Acute and Chronic Glomerulonephritis.*—It is a common observation that acute glomerulonephritis does not often pass into the chronic form. Volhard and Fahr state that the majority of acute cases recover in days, weeks or months according to their severity, and that only the very severe die. Of their seventy-one acute cases three became chronic. One of their patients developed acute nephritis in 1903, fourteen days after an attack of tonsillitis. In 1906 edema of the legs developed and never completely disappeared. In 1910 he had a typical chronic nephritis. Death in 1913. Duration, ten years.

Aufrecht[34] gave a very thorough description of a case of twenty years' duration which began acutely six months after an attack of scarlet fever. Albumin was found in the urine almost constantly throughout the illness. The patient had seven attacks of hematuria, one or more years apart, usually following inflammations of the throat. During the last six months the symptoms were very severe. At necropsy contracted kidneys and an enlarged heart were found.

34. Aufrecht: Eine zwanzig Jahre dauernde Nephritis nach Scharlach, Deutsch. Arch. klin. Med. **42**:517, 1888.

Mann [35] described a very similar case of twenty-eight years' duration, which was under his observation the entire period. An acute nephritis began in 1866 at the age of 14 years, following an attack of scarlet fever. The acute symptoms subsided in a few weeks and the patient regained her health, except that albumin continued to be present in the urine. For seven or eight years after the original attack the patient had occasional subacute attacks some of which were accompanied by edema. Attacks usually followed exposure to cold and usually lasted two or three weeks. From 1880 on the urine became of lower specific gravity and increased in amount. Arterial tension gradually rose. Retinal hemorrhages and uremia preceded death in 1894. At necropsy the heart was found hypertrophied. The kidneys were contracted, each weighing about 2 ounces.

Löhlein had a case in which the acute attack occurred in 1894 at the age of 16 years. The patient spent 1897-99 in the army. In 1901 he developed symptoms of contracted kidneys and died with anuria, severe edema and uremic symptoms. Löhlein believes that a chronic nephritis "not very rarely" develops from an acute nephritis of scarlet fever or angina.

Eichhorst [36] reported two cases of intermittent albuminuria of several years' duration which followed scarlet fever. The patients finally recovered. Another of his patients developed a hemorrhagic nephritis on the fourth day of an acute tonsillitis. He still had blood, casts and albumin in the urine two years later.

Sorensen and Volhard and Fahr believe that scarlet fever is rarely responsible for a chronic nephritis. Reichel says "numerous observations show that a chronic nephritis may develop from a scarlatinal nephritis."

Ernberg [37] located forty of 106 adults who had had acute nephritis before the age of 15 years, and found normal urine in all. In sixteen of fifty adults who had had acute nephritis between the ages of 15 and 30 years he found normal urines in all but four.

Reports on soldiers who have had acute nephritis (war nephritis) show that many of them have not recovered completely (Robinson,[38] Patterson [39]). There are indications that some of these men will develop chronic nephritis.

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35. Mann, J. D.: On Granular Kidneys Following Scarlatinal Nephritis, Lancet **2**:670, 1895.

36. Eichhorst, H.: Ueber chronische intermittierende Albumenurie als Nachkrankheit infektioser Nephritiden, Med. Klin., 1919.

37. Ernberg (cited from Hill): Boston M. & S. J. **177**:313, 1917.

38. Robinson, A. R.: The After History of War Nephritis, J. Roy. Army Med. Corps **30**:205, 1918.

39. Patterson, D. W.: British M. J. **2**:431, 1921.

Our Cases 48 to 51 are apparently examples of chronic glomerulonephritis developing from acute cases. It is possible that in Case 48 the sudden onset of symptoms was due to a severe exacerbation of a chronic nephritis and not to a primary acute attack. In Case 51 there is abundant microscopic evidence of an old attack of acute interstitial nephritis such as occurs in scarlet fever, and this observation is strong support for the assumption that his weakness after scarlet fever was due to nephritis. Cases 50 and 51 seem to be clean cut cases.

The evidence accumulated shows that a chronic nephritis may develop from a typical acute case but that such instances are rare. The great majority of acute cases do not terminate in chronic disease, and the great majority of chronic cases do not begin as clinical acute nephritis. But this does not exclude the origin of chronic nephritis from a "clinically veiled" acute case, as Löhlein has expressed it. It is conceivable and even probable that an infection of slow development may occur without producing intense clinical symptoms. If edema failed to develop there would be a striking change in the clinical picture.

The clearly established fact that an occasional case of chronic nephritis does develop from an acute case seems to prove that at least a few cases of chronic nephritis are due to infection, since the infectious nature of the acute type can hardly be denied.

2. *The Blending of the Different Clinical Types of Glomerulonephritis.*—It is maintained by some observers that chronic nephritis has very little clinical resemblance to the acute type and might therefore have a different etiology. But such a view encounters difficulties when a large series of cases is studied. Senator was impressed with the fact that the nephritides form a continuous group with numerous intermediate cases between the acute and chronic types. The recognition of a subacute type by most observers is a further support of this view.

Nine of our cases (Cases 33 to 41) have been classed as subacute, but some of these might be considered acute by other observers. Cases 42 to 45 show structural changes somewhat more advanced than the subacute group but much less advanced than the typical chronic case. Case 43 was of at least one year's duration. This group (Cases 33 to 45) seems to us to illustrate gradual transitions between acute and chronic nephritis.

3. *Associated Infections.*—In the subacute group there are several cases with evidence of a preliminary infection. Case 33 began with acute pericarditis, traces of which were found at necropsy. Case 38 followed a cold and bronchitis which was apparently due to wetting of the feet. Old healed endocardial lesions were found in Case 33. In Case 35 there was jaundice early in the disease and a seropurulent

pleuritis was found at necropsy. In Case 36 symptoms of nephritis appeared three days after an injection of neo-diarsenol. There was a severe attack of arthritis in Case 41 four months before death, and thrombosed pelvic veins were found in Case 37. Ophüls found in most of his subacute cases a comparatively recent history of tonsillitis, rheumatism or other streptococcic infection.

In the chronic group there were sixteen cases without history of a primary infection and without associated old infections at necropsy. The clinical data in some of these were, however, incomplete. In the other cases there was some evidence of a primary infection. Old healed mural or valvular lesions were found twice (Cases 45 and 63). One patient (Case 52) had a chronic purulent otitis media of many years' duration, as well as frequent attacks of tonsillitis. Two other patients (Cases 54 and 62) gave a history of frequent attacks of tonsillitis. A number of the patients had had scarlet fever, and microscopic evidence of scarlatinal interstitial nephritis was found twice (Cases 51 and 60). The high incidence of tonsillitis and scarlet fever among persons who do not develop nephritis of course detracts from the value of our data. Two patients had had acute articular rheumatism (Cases 42 and 63). Four cases apparently followed acute nephritis.

On the whole, it may be said that the evidence of associated streptococcic infections is very convincing in the acute group, fairly good in the subacute, but not at all satisfactory in the chronic group. It does not seem to us that these data exclude the primary infection in the chronic case. The clinical data are often incomplete, the patient having forgotten things that happened several years before; or the primary infection may have been comparatively mild and ignored by the patient. The primary infection may heal in a short time. Even in acute cases following tonsillitis, the throat is usually about normal when the renal symptoms appear.

4. *Microscopic Evidence.*—The strongest argument for the infectious origin of chronic glomerulonephritis is obtained from microscopic study of the kidneys. Every abnormal glomerulus in a chronic kidney is readily explainable as the outcome of one or more acute inflammatory processes. The various forms of acute glomerulonephritis are recognizable in their healing stages in the chronic kidney, and sometimes even acute glomerular lesions are seen along with the chronic changes.

The proliferative form of glomerulitis is the most important since it causes permanent closure of the capillaries. When there is complete closure of all the capillaries in the acute stage (Fig. 5) the tubule atrophies rapidly and the glomerulus soon becomes small and hyaline. If, however, some of the capillaries are not closed the glomerulus continues to function to some extent and undergoes hyaline degenera-

tion only in the closed portions (Figs. 19 and 17). In chronic nephritis practically all the glomeruli are damaged by closure of part of the capillary network.

The epithelial crescents which characterize the extracapillary type of glomerulitis are easily recognized in chronic nephritis. When first formed the crescents are composed of cells with distinct nuclei and well stained cytoplasm (Fig. 8). On long standing they gradually become homogeneous and hyaline. All intermediate stages are recognizable (Fig. 15). Extracapillary lesions were numerous in five of the subacute cases. In the chronic group old crescents were found in twelve of twenty-eight cases. They were numerous in four, frequent in three, and rare in five cases. Epithelial crescents have been produced experimentally by bacterial inoculations (Pernice and Scagliosi [40]). Their presence in chronic nephritis is a strong argument for the infectious nature of this disease.

Exudative glomerulitis is characterized by polymorphonuclears in the capillaries, and when this is combined with the proliferative type the leukocytes become imprisoned in the closed capillaries (Figs. 12, 13 and 14). Frequently masses of polymorphonuclears are retained for an indefinite time in the lumina of tubules or in the interstital tissues. This gives another form of evidence by which we may prove that a previous acute infection was present.

Polymorphonuclears in closed glomerular capillaries were found in six subacute and thirteen chronic cases, sometimes in large numbers. Masses of pus cells were found in the tubules in six chronic cases. There were only seven chronic cases that had no epithelial crescents and no pus cells in glomeruli or tubules.

The histologic evidence is convincing that the glomerular lesions in chronic kidneys are the healing stages of acute lesions, and if one admits that acute glomerulitis is due to infection it is difficult to escape the conclusion that chronic glomerulonephritis is due to the same cause.

Progressive Character of Chronic Glomerulonephritis.—It is known that patients with chronic nephritis may live many years. A duration of ten years is frequently seen and Mann's patient lived twenty-eight years. During the course of the disease there may be long intervals when the patient is in good condition with only a trace of albumin in the urine and fairly efficient kidneys as shown by functional tests. But at irregular intervals acute exacerbations occur, characterized by the usual symptoms of renal insufficiency. The patient improves after many of these acute attacks but finally develops a permanent renal insufficiency which soon ends in death. These exacerbations are well

40. Pernice and Scagliosi: Beitrag zur Aetiologie der Nephritis, etc., Virchows Arch. f. path. Anat. **138**:521, 1894.

illustrated in the excellent case records published by Mann and Aufrecht. They seemed to be due usually to exposure to cold in Mann's patient and to throat infection in Aufrecht's. Emerson [41] has recently emphasized the importance of these acute exacerbations in causing progressive destruction of the kidneys. He attributes these exacerbations to infections, chilling of skin, errors in diet, too much exercise, etc., and believes that chronic nephritis is not necessarily a progressive disease.

Our clinical data are not complete enough to warrant an extensive analysis of this topic, but there are records of acute exacerbations in eight patients (Cases 48, 49, 51, 52, 53, 57, 59 and 69). In Cases 49 and 51 the exacerbations followed attacks of sore throat.

In Case 51, in addition to the chronic changes, a number of fairly recent glomerular lesions were found, which were in all probability due to the severe throat infection which developed two months before death. In Case 52 a chronic purulent otitis media was present. The kidneys of this patient showed abundant evidence of a recent infection, viz., acute glomerulitis, fresh purulent exudate, etc. In these two patients at least there is convincing evidence that fresh infection contributed to the destruction of the renal tissue. Löhlein mentions rare instances in which acute glomerulitis is found in chronic kidneys.

Both the clinical and the pathologic evidence, therefore, seem to support the view that the downward progress of chronic glomerulonephritis is largely due to recurring infection. These infections are probably not often focal in character, but it seems a reasonable inference that known foci of infection, such as diseased tonsils, abscessed teeth, etc., should receive attention. An effort should be made to protect the chronic nephritic against infection, but diseased glomeruli are abnormally sensitive to bacterial toxins and glomerular injury will probably occur no matter how careful the patient may be. Throat infections and exposure to cold are to be especially avoided. The influence of diet and excessive muscular effort in causing exacerbations is not well established.

In explaining the downward tendency of chronic nephritis after renal insufficiency has developed another factor should be considered. Dr. Hilding C. Anderson,[42] in some experiments carried on in this laboratory, has found that a permanent renal insufficiency may be produced by the surgical removal of about three-fourths of the renal tissue. In the course of a few weeks the kidney remnant undergoes degeneration which is not explainable on the basis of obstruction or infection and seems to be due to excessive functional strain. If these

41. Emerson, C. P.: The Acute Element in the Chronic Nephropathies, J. A. M. A. **77**:745 (Sept. 3) 1921.

42. This paper is being prepared for publication.

conclusions be correct they may be applied to the final stages of chronic nephritis in man.

Atrophy of the Renal Tubule.—Löhlein's interpretation of tubular atrophy as a disuse atrophy is in accord with our observations. From a study of serial sections it has been observed that the size of the tubule corresponds closely to the permeability of the glomerulus and that the tubule disappears when the glomerulus becomes completely hyalinized. It has been claimed that the atrophy of the tubule is due to inadequate blood supply because of the closure of the glomerular vessels; but one frequently sees atrophic tubules surrounded by well filled capillaries and there are free anastomoses between the capillaries of adjacent tubules. Besides, Dehoff [43] has shown that the terminal branches of the interlobular arteries pass directly to the capillary network of the tubules. Tubular atrophy occurs as readily at the surface of the kidney as elsewhere.

The evidence that chronic glomerulonephritis is due to infection may be summarized briefly as follows:

There is abundant clinical and pathologic evidence for the infectious origin of the acute type and good evidence for a similar origin of many subacute cases. When this is admitted there is no escape from the conclusion that the chronic type has a similar cause.

In our series there is a gradual transition from the acute through the subacute to the chronic type, and it is obvious that we are not dealing with different diseases. On clinical grounds alone a fundamental relationship between the different forms must be admitted.

An occasional acute case becomes chronic and it must be conceded that at least these chronic cases are due to infection. The structural changes in these kidneys are not different from those of other chronic cases.

The glomerular lesions in chronic kidneys are obviously healing and healed stages of acute glomerulitis. The old epithelial crescents and the closed capillary loops filled with disintegrated polymorphonuclears cannot be explained on any other basis.

Definite acute and subacute glomerular lesions are sometimes found in chronic kidneys. These cannot be satisfactorily explained except as exacerbations of an inflammatory process.

SUMMARY

Thirty-two cases of acute glomerulonephritis have been studied. In many of these cases death was due to extrarenal causes and early glomerular lesions are available for study.

43. Dehoff, E.: Die arteriellen Zuflüsse des Capillarsystems in der Nierenrinde des Menschen, Virchows Arch. f. path. Anat. **228**:134, 1920.

Degenerative, exudative and proliferative types of inflammation occur in the glomeruli. Proliferative changes are chiefly responsible for permanent glomerular damage.

Acute glomerulonephritis is nearly always due to some acute infectious process, usually a streptococcal infection. The bacteria gain access to the blood and it is probable that the injury is produced by the direct action of their bodies on the glomerular endothelium.

An occasional case of acute glomerulonephritis passes into the chronic form; but the great majority of chronic cases do not begin as frankly acute nephritis.

Acute glomerulonephritis is linked with the chronic form by numerous intermediate cases.

Glomerular lesions in chronic kidneys correspond to healing or healed stages of acute glomerulitis. Old epithelial crescents are common, and disintegrating polymorphonuclear leukocytes are frequently found in the closed glomerular capillaries and in the partially atrophied tubules. In a few chronic cases acute and subacute glomerular lesions were found, indicating acute exacerbations.

In chronic glomerulonephritis many glomeruli are obliterated completely and those persisting show permanent closure of a part of the capillary network. Function is carried on by damaged glomeruli, and is depressed not only because of reduction in the total number but also because of the reduced capillary network in those that persist.

The progressive nature of chronic glomerulonephritis is apparently due, in part, to repeated acute exacerbations.

All forms of glomerulonephritis are due directly to bacterial invasion of the glomeruli; and the various clinical and pathologic types depend on the degree and extent of the permanent glomerular injury.

BIOCHEMICAL STUDIES IN A FATAL CASE OF METHYL ALCOHOL POISONING*

I. M. RABINOVITCH, M.D.
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It is not sufficiently appreciated that methly alcohol is very toxic. For economic reasons, methyl (wood) alcohol is employed as a substitute for ethyl (grain) alcohol, in what may be termed comparatively innocent products, such as perfumes, hair tonics, skin lotions, polishes, varnishes, etc. Government analysts, not infrequently, find it employed in the manufacture of various extracts for the flavoring of food products. Since prohibition has come into force, pure methyl alcohol, being somewhat similar in odor and taste to ethyl alcohol, has been employed in the preparation of various alcoholic beverages. This in great part is due to ignorance and has resulted in many deaths.

The literature, both experimental and clinical, on this subject shows a preponderance of papers relative to the effects of this drug on the central nervous system, especially the brain and optic nerves, and little reference has been made to lesions elsewhere in the body. More recently the importance of an acidosis as the cause of the more general signs and symptoms in methyl alcohol poisoning has been emphasized.

Little consideration has, however, been given to the changes which may occur in the kidney and other functions which may be manifested by variations from the normal chemical composition of the blood. In the following case special attention was given to this.

REPORT OF CASE

History (Hosp. No. 4937/21).—A female, aged 70 years, was admitted to the medical wards of the Montreal General Hospital, into the service of Dr. H. A. Lafleur, with a history of having taken, with suicidal intent, Oct. 24, 1921, one drinking-glassful of wood alcohol. There was a history of vomiting prior to admission, but no vomiting occurred while she was in the hospital, a period of five days. On admission, the patient was drowsy and very much confused, so that it was not possible to obtain a detailed history.

Physical Examination.—The patient was a white female apparently of the stated age. There was slight cyanosis. The right pupil was larger than the left. Both reacted to light and accommodation. The tongue protruded in the midline with a slight tremor at the edges. There was a slight sweetish (acetone) odor to the breath. Physical examination otherwise was negative, with the exception of the fundi oculi. There was a slight effusion into the retina.

Course.—From the time of admission the patient grew progressively weaker. The respirations, at first of the Kussmaul (acidosis) type, became very

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shallow during the last two days. October 29 the cyanosis became more marked and there was clinical evidence of bronchopneumonia.

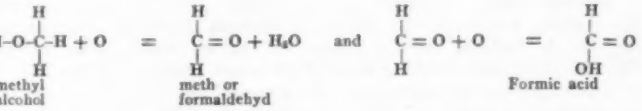
The patient was incontinent throughout her stay in the hospital, and it was not possible to obtain a specimen of urine at proper periods for chemical analysis. This was unfortunate as no examination could be made of the excretion of organic acids. A single specimen obtained by the house physician at the time of admission showed a clear urine, specific gravity 1.018, albumin 7.8 gm. per liter, many hyalin and granular casts, a few blood cells, and a trace of acetone. The accompanying table shows the combined results of the blood examination made every twelve hours during the patient's illness.

CHEMICAL ANALYSIS OF THE BLOOD

	Milligrams per 100 C.c.					CO_2	Per Cent.		Venous Oxygen		
Date	Uric Acid	Urea N	Creatinin	Sugar	Phosphorus	Volume	Hb.	mHb.	Content	Capacity	Unsaturation
Oct. 26, p.m.	3.1	42	1.6	...	....	46	..	..	...	....	....
Oct. 27, a.m.	5.3	102	2.3	...	....	29	..	..	...	....	....
p.m.	7.6	118	3.6	1822	8.8	39	..	..	...	....	....
Oct. 28, a.m.	8.4	130	4.0	223	11.2	34	..	..	...	....	....
p.m.	9.2	129	4.4	226	10.8	39	94	0	7.5	16.9	9.1
Oct. 29, a.m.	9.0	98	4.0	228	8.6	30	..	..	...	....	....
p.m. (3:30) 4 p.m. died	9.3	144	4.5	228	9.9	28	90	0	2.6	16.8	14.2

DISCUSSION

It has long ago been demonstrated[1] that the difference in the character and degree of intoxication between ethyl and methyl alcohol is due to the fate of these substances following their administration. Ethyl alcohol is oxidized into easily excreted products, carbon dioxid and water. Methyl alcohol is, however, only partially oxidized. The products of this incomplete oxidation being meth or formaldehyd and formic acid.



These partially oxidized substances are very toxic. It has been found[2] that formic acid is six times as toxic, and formaldehyd[1] is thirty-three times as toxic as methyl alcohol. Thus, from the oxidation of a toxic substance, products may result which are many times more toxic. This has an important bearing in the interpretation of the blood analysis.

1. Hunt, R.: The Toxicity of Methyl Alcohol, Johns Hopkins Hosp. Bull. **13**:2, 213, 1902.

2. Gettler, A. O., and George, A. V. St.: Wood Alcohol Poisoning, J. A. M. A. **70**:145 (Jan. 19) 1918.

KIDNEY FUNCTION

In experimental work with methyl alcohol changes in the kidney have been noted. Tyson and Schoenberg [3] in work on dogs found at necropsy dark purple and congested kidneys. Gettler [2] in one case, found marked parenchymatous degeneration of the kidneys. An analysis of the chemical findings of the blood in our case with reference to the urea nitrogen, uric acid, creatinin and phosphorus shows that rapid changes occurred in the kidney function. The uric acid content increased from 3.1 to 9.3 mg. per hundred c.c. in less than six days. The urea nitrogen content increased from 42 to 144 mg. per hundred c.c., and the creatinin content from 1.6 to 4.5 mg. per hundred c.c. blood in the same period. The acid soluble phosphorus varied from 8 to 11 mg. per hundred c.c. blood calculated as phosphorus (P). So far as we know only one other case has been studied from this viewpoint, that of Harrop and Benedict.[4] Their findings differ entirely from ours. These authors found that the urea content of the blood was normal at one period, but remarkably low at another, 0.091 gm. per liter. This would correspond to 4.2 mg. urea nitrogen per hundred c.c. blood, which is exceedingly low. The blood phosphorus in their case was normal (3 mg. per hundred c.c. blood). Their patient recovered.

The initial high findings in our case may have been due to a previously existant chronic nephritis. There can, however, be no doubt that the rapid changes noted daily were due to the action of the poison. Such findings suggest a complete "renal block," and correspond to those occasionally found in the acute retention as seen in hypertrophy of the prostate, or the anuria of mercuric chlorid poisoning. That the kidney function was practically nil is also supported by the rapid increase in the uric acid and creatinin content of the blood. The patient took no food during these few days of illness. It may, therefore, be assumed that all the uric acid found was of an endogenous origin. If it is assumed that the average daily excretion (endogenous) of uric acid is between 100 and 200 mg., and that this amount is not excreted but is distributed throughout the blood, it will account for the daily increase noted. The anatomic findings appear to corroborate this view.

BLOOD SUGAR

Hyperglycemia was present throughout the course of the disease. The lowest concentration of sugar, found at the first examination, was

3. Tyson, H. H., and Schoenberg, M. H.: Experimental Researches in Methyl Alcohol Inhalation, J. A. M. A. **63**:915 (Sept. 12) 1914.

4. Harrop, G. A., and Benedict, E. M.: Acute Methyl Alcohol Poisoning Associated with Acidosis, J. A. M. A. **74**:1 (Jan. 3) 1920.

0.182 per cent. This gradually increased to 0.228 per cent. These findings seem difficult to interpret. Apparently, they can be attributed to the impairment in the kidney function, for such findings are not infrequent in advanced cases of chronic nephritis. It might, however, be assumed that the figures do not represent glucose, for the reason that on theoretical grounds methyl alcohol is oxidized to formaldehyd, and the latter is a reducing agent. Part of the reduction of the cupric oxid in the test might therefore be attributed to the presence of this agent. Virtually, however, it does not seem that this occurred. The studies of Denis and Aldrich,[5] who employed liquor formaldehyd for the preservation of blood specimens, show that the addition of this drug in certain amounts does not alter the results obtained in blood sugar estimation. Even if we assume that all the methyl alcohol taken by this patient was completely oxidized to formaldehyd and distributed throughout the body, its concentration in the blood would not reach the percentage that these authors found could be added to blood without interfering with the chemical estimation of sugar. An interesting observation of these same authors is that liquor formaldehyd prevents glycolysis for at least ninety-six hours in vitro. That this should occur in vivo is only conjectural. The impairment of the kidney function seems sufficient to account for the hyperglycemia noted.

ACIDOSIS

The plasma carbon dioxid combining power on admission was 46 volumes per cent. It eventually fell to 26 volumes per cent. Other factors which may lower the carbon dioxid combining power of the blood, such as increased pulmonary ventilation having been excluded, it may be assumed that an acidosis existed. An acidosis has previously been demonstrated [6] in the study of methyl alcohol poisoning.[6] It has, however, been attributed to the failure of the body to completely oxidize methyl alcohol with the production of formic acid. The acidosis has been found [7] to be associated with an increase in the excretion of organic acids, lactic and formic. In our case the retention of phosphates in the blood would also explain part of the acidosis.

It does not appear to be unreasonable, on theoretical grounds, to suggest that the acidosis may, in large part, be due to the formation in the body of methylene derivatives, from the action of the formaldehyd on the amino-acids present. These derivatives are more

5. Denis, W., and Aldrich, M.: Note on the Preservation of Specimen of Blood Intended for Blood Sugar Estimation, J. Biol. Chem. **44**:203 (Oct.) 1920.

6. Haskell, C. C.; Hileman, S. P., and Gardner, W. R.: The Significance of the Acidosis of Methyl Alcohol Poisoning, Arch. Int. Med. **27**:71 (Jan.) 1921.

7. Van Slyke, D. D.: Studies of Acidosis, J. Biol. Chem. **41**:567 (April) 1920.

strongly acid in reaction owing to the destruction of the basic properties of the amino group, and, therefore, should effect the acid base equilibrium of the blood. Such a reaction is readily demonstrated in vitro. The Henriques-Sörensen formol titration of amino-acid nitrogen is based on this principle [8] as is shown in the following equation:

$$\begin{matrix} R.\ CH.\ NH_2 \\ | \\ COOH \end{matrix} \quad +6CH_2O = \begin{matrix} R{-}CH{-}N{:}\ CH_2 \\ | \\ COOH \end{matrix} \quad +H_2O$$

Also the production of free acids from the action of liquor formaldehyd on neutral ammonium salts in the body does not seem unreasonable and may explain part of the acidosis, as is shown in the following equation:

$$4\ NH_4Cl + 6\ CH_2O = N_4(CH_2)_6 \quad + \quad 6\ H_2O + 4\ HCl$$

An interesting observation along these lines is that of Gregnolo who found after the injection of methyl alcohol there was an increase in the hydrogen ion concentration of the serum.

CYANOSIS

From the time of admission to the hospital the patient exhibited a definite cyanosis. This was very slight at first, but became more marked during the progress of the disease. Very little reference to biochemical studies could be found in the literature on the relation between methyl alcohol poisoning and cyanosis, although this relation has frequently been noted clinically. An effort was made to determine the cause in our case. An analysis was made of the oxygen content, oxygen capacity and oxygen unsaturation of the blood.

It might be recalled that the oxygen content represents the total oxygen combined with hemoglobin, and otherwise, circulating in the blood at the moment and site of withdrawal. The oxygen capacity represents the total oxygen the blood could hold if it were completely saturated with oxygen. The oxygen unsaturation [9] represents the difference between the oxygen capacity and content. The method employed for the estimation of the oxygen was that of Van Slyke.[10] It has been shown [11] that if the blood is completely saturated with oxygen in the lungs, the oxygen unsaturation of the venous blood may increase from 13 to 14 volumes per cent. before cyanosis appears. If it appears at less than this figure arterial unsaturation may be assumed. It will be noted in the chart that at the first estimation the oxygen

8. Hawk: Practical Physiological Chemistry, Ed. 6, Philadelphia, P. Blakistons Sons Co., p. 526.

9. Lundsgaard, C.: Studies of Oxygen in Venous Blood, J. Biol. Chem. **33**:133, 1918.

10. Van Slyke, D. D.: Gasometric Determination of the Oxygen and Haemoglobin of Blood, J. Biol. Chem. **33**:127, 1918.

11. Lundsgaard, C.: Studies on Cyanosis, J. Exper. M. **30**:271 (Sept.) 1919.

unsaturation was 9 volumes per cent. Assuming, therefore, that arterial unsaturation may have existed, the cause of this under the circumstances (poisoning) was problematic.

An analysis of the daily clinical notes showed that no gross changes occurred in the respiratory or circulatory systems. Although no gross clinical changes need be evident, and still certain conditions may exist which prevent complete oxidation of the blood, it seemed important to determine whether any chemical alteration had occurred preventing the blood from taking up its normal load of oxygen. Stadie [12] pointed out that there are many substances which in vitro readily produce methemoglobin. These include certain oxidizing agents, reducing agents, organic bases, salts and bacteria. It will be noted in the chart that during the first examination of the blood for methemoglobin none could be found. The method employed was that of Stadie.[13]

The cyanosis gradually became more marked, and on the following day definite changes (bronchopneumonia) were found clinically in the lungs. The blood examination one half hour before death, at which period there was a very marked degree of cyanosis, also did not show the presence of methemoglobin. At this time the oxygen capacity was practically normal. It may, therefore, be assumed that in the case studied either no methemoglobin was formed, or that it was eliminated as rapidly as it was formed and played no important part in the production of the cyanosis.

REPORT OF POSTMORTEM EXAMINATION

Pathologic Report.—Acute parenchymatous nephritis; cloudy swelling of the heart and liver; bronchopneumonia.

DETECTION OF METHYL ALCOHOL IN THE BODY TISSUES

Experimentally it has been found that when methyl alcohol is given per rectum it is excreted by the stomach. It has also been demonstrated that the stomach may excrete methyl alcohol unchanged for a considerable time. It has been assumed [2] that the alcohol has a selective action for brain tissue. The brain in every one of six cases analyzed by this author was found to contain this alcohol. For these reasons both the brain and stomach tissues were analyzed in our case.

After a critical study of the fifty-eight methods proposed for detecting methyl alcohol, Gettler [14] classified them in order of their

12. Stadie, W. C.: Studies on Blood Changes in Pneumonoccic Infections, J. Exper. M. **33**:627 (May) 1921.

13. Stadie, W. C.: A Method for the Determination of Methaemoglobin in the Blood, J. Biol. Chem. **41**:237 (Feb.) 1920.

14. Gettler, A. O.: Critical Study of Methods for the Detection of Methyl Alcohol, J. Biol. Chem. **42**:311, 1920.

efficiency. Those accepted as reliable, extremely sensitive, and involving little technical difficulty were employed. The method employed in this case is based on the oxidation of the methyl alcohol into formaldehyd and the detection of the latter by various color reactions. Potassium bichromate and concentrated sulphuric acid was used as the oxidizing agent. In detail the method was as follows:

Method.—In order to preserve the stomach contents the stomach was tied off at the cardiac and pyloric ends and removed in toto. This was then passed through a meat grinder and minced to a fine pulp. This pulp was then placed in an 800 c.c. Kjeldahl flask to which was added 400 c.c. water and sufficient concentrated sulphuric acid until a distinct acid reaction was obtained. This was then distilled and 200 c.c. of the distillate was neutralized to phenolphthalein with tenth normal sodium hydroxid and acidified with 5 c.c. of concentrated sulphuric acid, cooled, and 0.1 gm. potassium bichromate added and dissolved. This was then redistilled. To this final distillate the various color tests were applied.

1. To 3 c.c. distillate was added 5 c.c. concentrated sulphuric acid. This was cooled. The addition of a few milligrams morphin sulphate yielded a violet color. Test positive.

2. Test 1 was repeated with the morphin replaced by apomorphin. A violet color resulted. Test positive.

3. To 3 c.c. of the distillate were added two drops of a 2 per cent. solution of phenol. This was stratified on a layer of concentrated sulphuric acid. A red ring was noted at the junction of the two fluids. Test positive. Methyl alcohol was thus detected in the body tissues six days after its ingestion.

SUMMARY

In a fatal case of methyl alcohol poisoning changes had occurred in the renal and other functions as evidenced by variations from the normal chemical composition of the blood. These, in themselves, disregarding other well known factors, may account for the actual cause of death. Methemoglobin played no important part in the production of the cyanosis noted. Methyl alcohol could be detected in the tissues examined six days after the ingestion of the drug.

REVERSED RHYTHM OF THE HEART*

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I purpose, in this communication, to emphasize the distinction that should be made between the terms "reversed mechanism" and "reversed rhythm" of the heart.

The term "reversed mechanism" should be confined to express a reversal of the mechanism of impulse formation and conduction. Normally, the impulse originates in the sinus and traverses the auricles to be conducted through the auriculoventricular junctional tissues into both ventricles. In reversal of the mechanism, the impulse first originates in the auriculoventricular node, or the junctional tissues, or at a lower level in the heart and travels backward into the auricular musculature. Thus the term "reversed mechanism" implies a direction of stimulus conduction opposite to the normal.

Illustrative of such cases may be mentioned instances of auriculoventricular rhythm. In these cases, a ventriculo-auricular (R-P) interval may be exhibited with inversion or distortion of the auricular (P) wave. Williams and James,[1] Heard and Strauss,[2] White,[3] and Robinson and Draper[4] have recorded cases of this type. Cohen and Fraser[5] reported a case in which auricular contractions, represented by an inverted P wave, resulted from the mechanical stimulus received from the contracting ventricles. Wilson[6] reported a case of ventricular extrasystoles transmitted to the auricles.

From the experimental side, a great deal of work has been done on the subject by Lewis and his collaborators,[7] Eyster and Meek,[8] Meakins,[9] Wilson[10] and others.

The term "reversed rhythm," on the other hand, does not attempt to interpret the direction of stimulus conduction. It expresses only a time relationship between the ventricular and auricular contractions, i. e., the ventricular beat immediately precedes the auricular beat.

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* From the Department of Cardiovascular Diseases, Beth Israel Hospital.

1. Williams, H. B., and James, H.: Heart **5**:109, 1913.
2. Heard, J. D., and Strauss, A. E.: Am. J. M. Sc. **155**:238, 1918.
3. White, P. D.: Arch. Int. Med. **16**:517 (Nov.) 1915.
4. Robinson, G. C., and Draper, G.: Heart **4**:97, 1912.
5. Cohen, A. E., and Fraser, F. R.: Heart **5**:141, 1913.
6. Wilson, F. N.: Heart **6**:17, 1915.
7. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, Chapters XV and XIX, 1920, Paul B. Hoeber, New York; Lewis, White and Meakins: Heart **5**:289, 1913; Lewis and White: Heart **5**:335, 1913.
8. Eyster and Meek: Heart **5**:227, 119, 1913.
9. Meakins, J.: Heart **5**:281, 1913.
10. Wilson, F. N.: Arch. Int. Med. **16**:989 (Dec.) 1915.

This includes not only the cases of reversed mechanism, but also those cases in which the mechanism is normal, yet in which the ventricular contraction is delayed and, therefore, is grouped together with the following auricular contraction. In these cases, the auriculoventricular node discharges its impulse, in point of time, ahead of the sinus node, yet without reversal of the mechanism.

The case reported by Norrie and Bastedo [11] and entitled by them "reversed rhythm of the heart" is probably not, as they believed, a case of reversed mechanism. It is a case of heart block due to digitalis in which the beat of the auricle followed that of the ventricle. Their explanation that in their case, "the impulse to beat arises in the ventricle instead of at Keith's node and is conducted along the auriculoventricular bundle in a direction the reverse of normal" leaves room for question. Their published polygraphic curves might be interpreted as delayed P-R conduction, the auricular waves being related to the following ventricle. Thus their case is one of reversed rhythm, but probably not of reversed mechanism.

Lewis [12] described a case of premature beats arising in the a-v tissues in which the P wave was upright and of normal contour. From this fact, together with the varying P-R intervals, he concluded that the auricles were responding to the normal pacemaker while the ventricles were responding to an impulse arising low in the auriculoventricular bundle.

In Cushny's [13] earlier observation that reversed mechanism can be produced by injecting aconitin into the circulation of dogs, no electrocardiograms were recorded. In two instances, Cushny expressed the possibility that reversal of the rhythm may have occurred without reversal of the mechanism.

I desire now to give the observations in a case that presents periods of reversed rhythm without reversal of the mechanism and various features of interest associated with transitory partial heart block.

REPORT OF CASE

H. T., Russian, aged 46, gave a negative family history.

Past History.—He had measles and scarlet fever in childhood and occasional attacks of tonsillitis since. When he was 36 years old, he passed minute urinary calculi. The last attack occurred when he was 39 years old. His habits were good and he denied venereal disease.

Present Illness.—His present illness began when he was about 40 with a feeling of "heartburn" after meals which was relieved by sodium bicarbonate. For six months he had slight precordial pain which was worse with psychic depression. He had hunger pains during sleep and a pressing sensation in the

11. Norrie, V. H., and Bastedo, W. A.: St. Luke's Hosp. M. & S. Rep. No. 2.
12. Lewis, T., and Allen: Am. J. M. Sc. **145**:667, 1913.
13. Cushny: Heart **1**:1, 1909.

chest. At times, he had a feeling of choking and a feeling of dizziness lasting fifteen minutes together with a tingling sensation, as he described it, in the precordium and below the angle of the left scapula.

Physical Examination.—He had large follicular tonsils. His heart showed no enlargement, and no murmurs or accentuations were audible. The muscular quality of the first sound was deficient at the apex. The apex beat and the

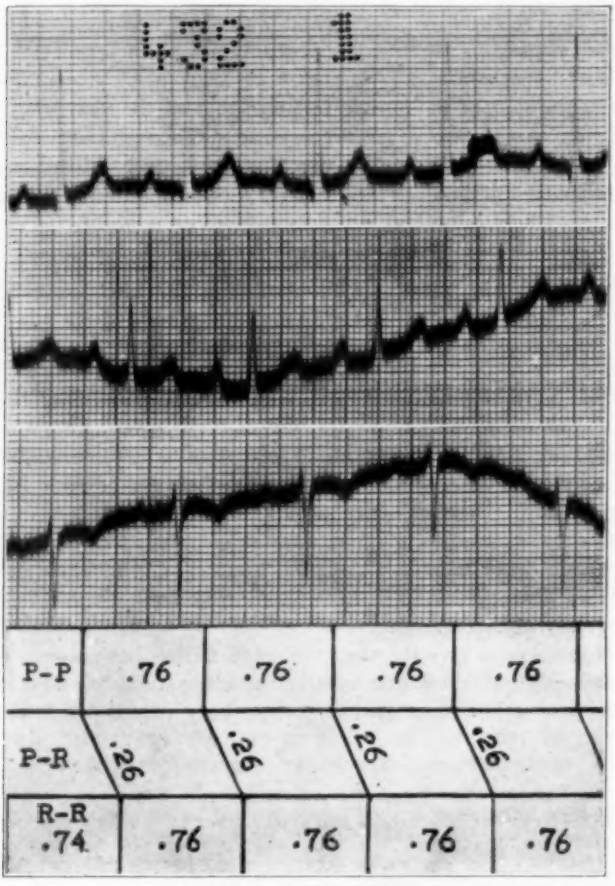

Fig. 1.—Showing a period of normal auricular and ventricular sequence and normal rhythm.

first sound, on the first examination, were distinctly and audibly alternans in character, and visibly so over the jugular. (This is explained later by the electrocardiograms.) Respiration increased the heart rate. Exercise increased it with some irregularity, the nature of which it seemed impossible to ascertain from physical signs alone and even from polygraphic tracings alone. Strenuous

exercise was tolerated without discomfort and produced no abnormal pulse or blood pressure reactions.

The urine was negative.

Cardiographic Studies.—The cardiograms show, at times, a regular heart with the normal auricular and ventricular sequence and normal rhythm (Fig. 1). The sinus rate is 79 a minute and the conduction

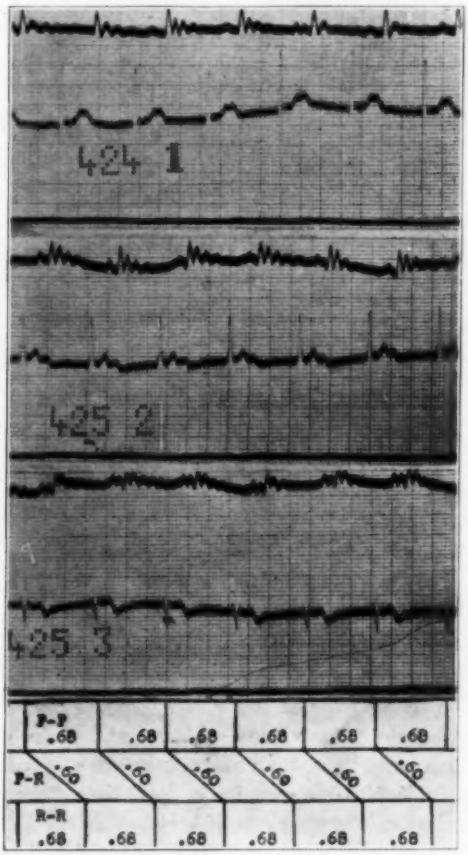

Fig. 2.—Showing delayed P-R conduction, with grouping of the R, P and T waves. Jugular tracing above and radial below.

between auricles and ventricles is 0.26 of a second. The only significant abnormality is the inversion of the T wave in Lead III.

The normal rhythm, however, is not permanent and can be easily disturbed by various influences which act on the circulation, on the myocardium and on the vagus nerves.

The conspicuous change that at times seems to occur spontaneously, and can easily be induced, consists of a moderate degree of sinus irregularity and a delay in conduction of the stimulus from the auricle to the ventricle. This is illustrated in the first cardiogram taken (Fig. 2). In this record, the action is regular. The auricular (P) wave is followed by the ventricular stimulus after a delayed conduction of 0.60 of a second. As the interval between beats is only slightly more than this (0.68 of a second), the P wave immediately succeeds the R and gives the picture of reversed rhythm where the R, P and T are grouped together in this respective order. The P wave is upright and normal in its contour.

The carotid wave is 0.18 of a second after the beginning of the Q R S wave. The auricular wave is seen 0.18 of a second after P and is very prominent because it contracts during ventricular systole and

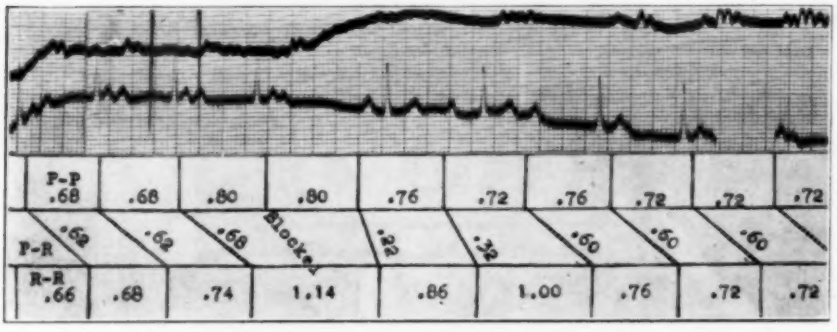

Fig. 3.—Showing the effect on the heart mechanism of taking a deep breath. The two vertical lines are the signal.

forces the blood back into the jugular veins. From the jugular tracing alone, the record could not be interpreted correctly. The carotid (c) wave would be thought to be the auricular wave and the following auricular wave would be considered ventricular because of the correct time relation between them and of their relative prominence. This record peculiarly demonstrates the indispensability of the electrocardiographic record in the interpretation of certain cases.

Effect of Vagus Stimulation.—The record following is a continuation and shows the effect on the heart mechanism of taking a deep breath indicated by the signal in Figure 3. The sinus is promptly slowed and there is a delay in conduction; the latter effect, on the junctional and bundle tissues, predominating and producing transient heart block. This is illustrated by the figures in the subjoined table showing the time relations between the various waves. The first

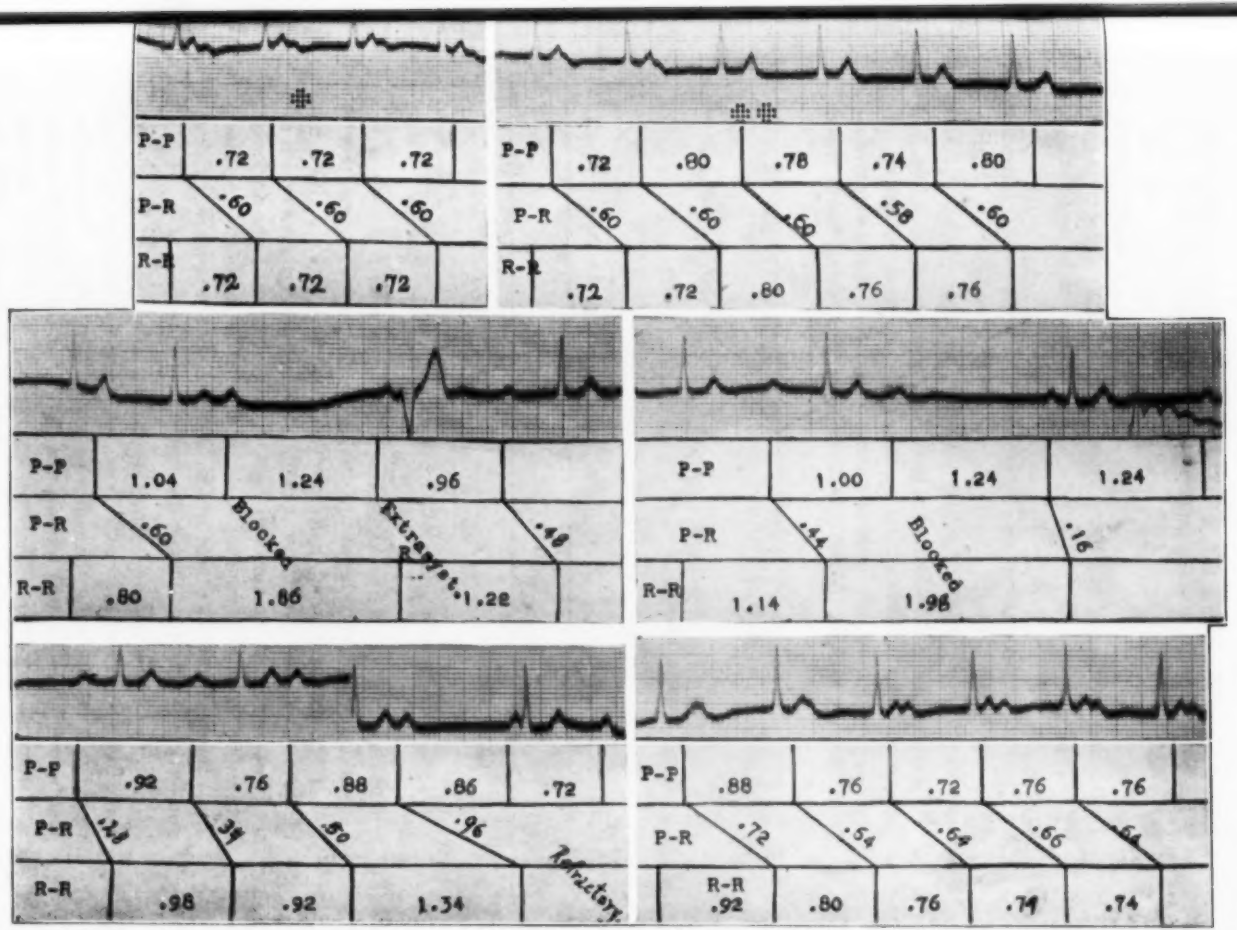

Fig. 4.—Showing the cycle of events during continued ocular pressure.

P wave after the signal is blocked, and in the following cycles, conduction, after having recovered, increases progressively until it is again 0.60 of a second.

Ocular pressure had a very similar, but much more marked effect. The sinus slowing and the heart block increased with the increase of pressure. One ectopic ventricular escape occurred after a period of block.

The cycle of events during continued ocular pressure is illustrated in the series of strips in Figure 4, the original reversal of rhythm returning after the effect of ocular pressure subsided.

Effect of Exercise.—During a period of normal rhythm (Fig. 1), the patient was instructed to exercise, the exercise consisting of hopping on one foot one hundred times. After this, the electrocardiogram showed a slight increase in the rate of the beat. About three

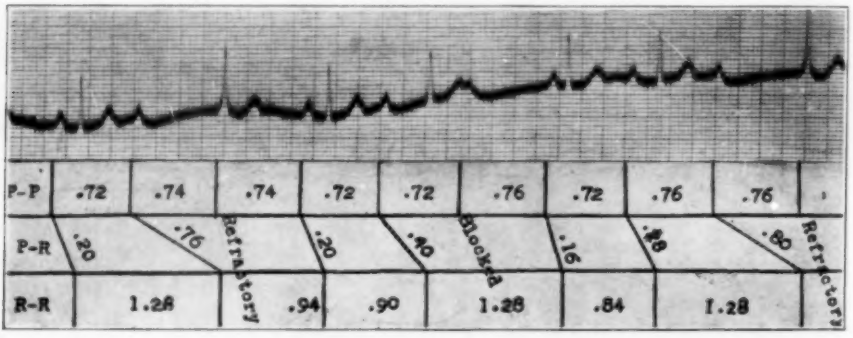

Fig. 5.—Showing the progressive increase of the block after exercise.

minutes after the exercise, while the patient was seated, the property of conduction suddenly began to show easy fatigue. A normal cycle took place with a normal P-R interval. The next cycle showed an increased P-R interval; the next might show a still further increase in the block and finally an auricular beat would be blocked or an auricular beat might occur simultaneously with a delayed ventricular beat; after this a repeated auricular beat would be promptly transmitted, conduction having recovered. This is illustrated in Figure 5.

Effect of Amyl Nitrite.—Amyl nitrite was administered by inhalation after a sufficient amount of rest following the exercise. A long record was taken during the entire period of inhalation. The rhythm just before inhalation was found to be normal and the amyl nitrite did not affect this rhythm. There was practically no increase in heart rate. As is usual, it depressed the height of the T wave. With the

elimination of its effect, the T wave returned to its previous height and a distinct U wave became evident. There was no evidence of difficult conduction.

Effect of Atropin.—When the effect of amyl nitrite had subsided and the rhythm was still normal, atropin, 1/150 grain, was given hypodermically. The first record was taken twenty-five minutes after this. There became evident a sinus irregularity and a marked difficulty of conduction, a normal conduction period being followed by a prolonged period or by a blocked cycle. No a-v nodal beats developed. Sixty minutes after the atropin was given, a record showed less difficulty in conduction than before. In Lead I, taken first, a normal cycle was followed by cycles in which conduction was progressively prolonged and every fourth cycle was blocked. In Leads II and III taken immediately after, the prolonged conduction became constant at 0.46 of a second, the heart rate being eighty-three a minute; i.e., the P-P and R-R intervals were 0.72 of a second.

This case is evidently an early case of heart block with periods of normal conduction and an instability of the normal rhythm. The important question to determine is whether the defect in conduction is due to nervous influences or is more definitely organic, due to disturbances in circulation or disease of the myocardium.

The features that incline one to the latter supposition are: (1) The stimulation of the vagus produces a temporary moderate, but not constant, increase of the block: i.e., the vagus influence superimposes itself on some other basis which continues to act after the vagus stimulation has subsided; (2) the depression or paralysis of the vagus by atropin does not completely relieve the difficulty in conduction; (3) exercise, accelerating the heart, seems to have a beneficial effect on conduction, perhaps by improving the cardiac circulation; (4) the electrocardiogram shows inversion of the T wave in Lead III.

The tracings and the record of this case emphasize the distinction that should be made between reversed mechanism and reversed rhythm and show the importance of electrocardiographic analyses.

SOME OBSERVATIONS ON PAROXYSMAL RAPID HEART ACTION WITH SPECIAL REFERENCE TO ROENTGEN-RAY MEASUREMENTS OF THE HEART IN AND OUT OF ATTACKS *

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With the application of the more accurate means of clinical investigation in the past decade, some of the views previously held concerning pathologic processes necessarily have needed revision. This has been true particularly with regard to the disturbed mechanism of the heart beat ever since the recent interest in cardiographic work. There must take place also a similar revision of our views concerning cardiac dilatation when one applies, as a check to findings from percussion and palpation, measurements determined by roentgen-ray examination. Any clinician, who has confirmed the results as to the size of the heart determined by percussion and palpation, with roentgen-ray measurements, must feel somewhat doubtful in detecting changes in the heart size of less than 1 cm., and not infrequently he will find that his bedside figures are at a considerably greater variance from the roentgenogram.

A further point that seems rather hazy in the minds of many students is the matter of dilatation of the heart. Possibly, the comparison to an elastic sac expanding and contracting unconsciously has led us to think of the heart in similar terms. For some reason there is a common belief that the heart frequently dilates, and as the clinical condition improves this dilatation disappears. The absolute proof that this is a common occurrence in cardiac patients is lacking, for most of the observations are made by the ordinary methods of inspection, palpation, percussion and auscultation and not confirmed by roentgen-ray examination. No doubt, the former methods are quite sufficient in the great majority of cases for the proper clinical management of the patient, but they are insufficient for the establishment of reliable scientific data on which to base our knowledge.

It is with this purpose in mind that roentgen-ray observations were made on eleven patients during attacks of paroxysmal rapid heart action and after the heart had returned to normal rhythm. These conditions have frequently been regarded as instances of acute dilatation

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of the heart, especially before cardiographic studies enabled us to classify and describe them properly. Mackenzie[1] says:

> Even more striking because more sudden and violent, are the changes (meaning dilatation) that take place in certain cases of paroxysmal tachycardia. . . . I have seen these cases on several occasions shortly before an attack and watched the steady progress of the change. The hearts were normal in size, but in three hours' time the transverse diameter had increased by two inches, the face had become livid and the lips swollen. . . . In the course of twenty-four hours edema of the legs appeared and the liver became large. After some days the dropsy extended up the legs, the abdomen became distended and the urine scanty. With the cessation of the attack of paroxysmal tachycardia, the patients at once experienced relief, and in a few hours every vestige of heart failure had disappeared, and the heart itself returned to a normal size and rhythm. . . . I have seen many cases in which the inception of the nodal rhythm was followed by these changes.

Lewis,[2] writing on the effect of paroxysms of fast heart on the circulation, says:

> When the heart commences to beat more rapidly it decreases in size. Where the acceleration is great the arterial pressure falls considerably while the venous pressure rises; but with lesser degrees of acceleration the arterial pressure may remain steady or may actually rise a little. . . . But in long continued paroxysms, especially where the reserve power of the ventricular muscle is imperfect, the heart dilates, the fall of pressure is more profound and the blood stagnates in the heart and venous systems.

In this study are included eleven patients with paroxysmal rapid heart action, the clinical data of which are appended. Five had paroxysmal auricular tachycardia, three had paroxysmal ventricular tachycardia, one had paroxysmal auricular flutter and two had paroxysmal auricular fibrillation. In all cases the diagnosis of the type of disturbance was confirmed by electrocardiographic tracings. In order to determine whether the hearts dilated during the various upsets, roentgen-ray examinations were made while the rapid heart action was in progress and while the heart was beating at a normal rate. Measurements of the transverse diameter of the heart shadows were made, which with other details are given in Table 1. These examinations were made after the attacks had lasted varying lengths of time, in some instances days after the onset, in others an hour or so (Table 2).

It is not the purpose here to discuss the technic and details of the roentgenological methods of heart examination. The method most used in this country at the present time for the measurement of the heart shadow is the teleroentgenogram, or the seven-foot plate. The determination of slight or moderate degrees of cardiac enlargement presents some difficulty even by the roentgenological method, because the shadow on the plate is merely a silhouette and because of individual variations associated with sex, height, weight, habitus, etc. The "cardio-

1. Mackenzie, J.: Diseases of the Heart, Oxford University Press, 1908, pp. 199-200.
2. Lewis, T.: Osler and McCrae's Modern Medicine, 1915, p. 87.

thoracic ratio" has been proposed by Danzer [3] as a convenient standard for determining whether the heart shadow is larger than it should be for the particular individual. In a study of more than five hundred cases he found that normal hearts cast a shadow the transverse diameter of which is 50 per cent. or less of the internal diameter of the chest shadow measured at its widest point, usually about the level of the fifth interspace anteriorly. This relation of the shadow of the heart to that of the thoracic cavity he terms the cardiothoracic ratio. Allowing

TABLE 1.—ROENTGEN-RAY MEASUREMENTS OF THE HEART SHADOW

Case	Diagnosis	Date	Approx. Target-Plate Dist.	Before, During, After Attack	Measurements in Cm.					Change in Mm. with Attack
					M R	M L	T D	I D C	C-T R	
1	Paroxysmal auricular tachycardia	12/23/14	30 in.	During	5.4	10.2	15.6	30.5	54%	
		1/ 8/15	30 in.	After	2.8	10.0	12.8	32.0	40%	28
2	Paroxysmal auricular tachycardia	7/ 6/16	84 in.	During	5.9	9.2	15.1	26.0	58%	
		7/ 8/16	84 in.	After	5.6	10.1	15.7	26.0	60%	—6
3	Paroxysmal auricular tachycardia	12/13/16	84 in.	During	5.1	11.1	16.2	27.5	59%	
		12/13/16	84 in.	After	4.4	10.8	15.2	27.5	55%	10
4	Paroxysmal auricular tachycardia	11/ 6/19	84 in.	Before	3.8	5.5	9.3	20.5	45%	
		11/ 7/19	84 in.	During	3.5	6.3	9.8	20.5	48%	5
		11/10/19	84 in.	After	3.9	5.6	9.5	20.5	46%	3
5	Paroxysmal auricular tachycardia	6/ 9/20	84 in.	During	6.8	9.0	15.8	23.0	69%	
		6/12/20	84 in.	After	5.9	10.0	15.9	23.0	69%	—1
6	Paroxysmal ventricular tachycardia	9/ 5/15	30 in.	During	3.2	6.7	9.9	28.0	35%	
		12/ 2/15	30 in.	After	3.0	7.6	10.6	30.0	35%	—7(?)
7	Paroxysmal ventricular tachycardia	11/ 3/16	30 in.	During	5.0	11.4	16.4	31.5	52%	
		11/ 9/16	30 in.	After	3.8	11.9	15.7	30.5	51%	7
8	Paroxysmal ventricular tachycardia	1/ 5/20	84 in.	During	4.8	13.1	17.9	27.0	66%	
		3/ 9/20	84 in.	After	5.2	11.3	16.5	27.0	61%	14
9	Paroxysmal auricular flutter	10/21/14	30 in.	During	7.3	9.6	16.9	32.0	53%	
		10/29/14	30 in.	After	7.1	9.4	16.5	32.0	52%	4
		2/ 5/15	30 in.	During	6.5	9.3	15.8	30.5	52%	
		2/ 8/15	30 in.	After	6.4	9.3	15.7	30.5	51%	1
10	Paroxysmal auricular fibrillation	3/12/20	84 in.	During	4.5	8.6	13.1	21.5	61%	
		3/15/20	84 in.	After	4.0	8.6	12.6	21.5	59%	5
11	Paroxysmal auricular fibrillation	12/14/20	84 in.	During	4.9	9.4	14.3	24.5	58%	
		12/16/20	84 in.	After	5.1	9.7	14.8	24.5	60%	—5

Measurements: M R = distance from the median line to the point of the heart shadow farthest to the right; M L = distance from the median line to the point of the heart shadow farthest to the left; T D = transverse diameter of the heart shadow, i. e. M R plus M L; I D C = Internal diameter of the chest shadow at about the level of the left diaphragm; C-T R = cardiothoracic ratio = T D divided by I D C.

a margin of 2 per cent. for error, he believes the heart to be enlarged when this ratio is more than 52 per cent., but points out that enlargement cannot be ruled out when the figure is less than 52 per cent., particularly in the ptotic habitus. As both the size and shape of the chest and the size and position of the heart vary with the above mentioned factors, especially with the habitus, this seems to be the best

3. Danzer, C. S.: Cardiothoracic Ratio, An Index of Cardiac Enlargement, Am. J. M. Sc. **157**:513, 1919.

method at hand for the determination of slight or moderate degrees of enlargement. It has been used in this study as a check on the actual measurements in centimeters of the heart shadow, especially in those cases taken at a distance of about thirty inches, in three of which there was apparently enough variation in the distance to make a difference of 1 or 2 cm. in the internal diameter of the chest. In Case 6, for example (Table 1), the heart shadow itself measured 0.7 cm. more

TABLE 2.—CLINICAL DATA

Case	Med. No.	Age	Sex	Diagnosis	Wassermann	Symptoms of Heart Failure During Attack	Rate in Attack	Duration of Attack	Duration at Time of Roentgenoscopy	Dilatation
1	2092	38	M	Paroxysmal auricular tachycardia	—	Severe Severe	250 242	5 days 8 hrs.	3 days	Marked
2	4940	50	F	Paroxysmal auricular tachycardia, syphilis	++	Moderate	220	4½ da.	4 da.	None
3	5742	21	M	Paroxysmal auricular tachycardia, aortic insufficiency, mitral insufficiency, chronic myocarditis	—	Severe	162	Several hours	Few hours	Slight
4	12207	24	F	Paroxysmal auricular tachycardia, mitral stenosis	—	Moderate	233	2 hrs.	½ hr.	?
5	13577	50	F	Paroxysmal auricular tachycardia, chronic infectious arthritis	—	None	171	Several hours	2 hrs.	None
6	3324	64	F	Paroxysmal ventricular tachycardia, chronic myocarditis	—	Moderate	160	Several hours	Few hours	None
7	5503	50	M	Paroxysmal ventricular tachycardia, chronic myocarditis	—	Severe	160	Few hours	1 hr.	None
8	12646	64	M	Paroxysmal ventricular tachycardia, chronic myocarditis	—	Severe	165	36 hrs.	12 hrs.	Slight
9	1791	35	M	Paroxysmal auricular flutter, aortic stenosis and insufficiency	—	Slight Slight	178 178	12 da.+ 4 da.	11 da. 3 da.	None None
10	13074	38	F	Paroxysmal auricular fibrillation, mitral stenosis and insufficiency	—	Moderate	135	Several hours	1 hr.	None
11	*	26	M	Paroxysmal auricular fibrillation	..	Slight	120	2 da.	18 hrs.	None

* This was a private case of Dr. Paul D. White, Boston, who kindly offered it for use in this series, for which we wish to express our appreciation.

after than during the attack; but as the internal diameter of the chest shadow also was larger in the second plate, the cardiothoracic ratio was the same in both, showing that no definite change in the size of the heart shadow had taken place.

In the estimation of the size of the heart from its shadow on the plate three sources of error are to be considered: (1) magnification due to the divergence of the rays; (2) changes in the position of the

heart during the respiratory cycle, and (3) changes in the profile of the heart due to the fact that the chest is not pressed symmetrically against the plate during the exposure and spoken of as "rotation." It seems advisable to discuss these points very briefly.

The magnification due to the divergence of the rays is practically compensated for by increasing the distance between the target of the roentgen tube and the plate to approximately seven feet. The mathematically figured correction for the transverse diameter of the heart shadow taken at a target-plate distance of two meters, as given by LeWald and Turrell,[4] is 4 per cent., i. e., the true transverse diameter is 96 per cent. of that of the silhouette.

During ordinary quiet respiration the position of the heart changes very slightly, if at all. With full inspiration or forced expiration, however, there is a very marked change in the relation of the heart to the chest wall and in the physical axis of the heart, and consequently in the form and size of its silhouette. The transverse diameter of the heart shadow of one of us taken during quiet respiration at approximately 7 feet measured 14.3 cm., while that taken at the same distance but with full inspiration measured only 12.8 cm. At a thirty-inch distance with full inspiration the shadow was 14.1 cm. in diameter. Here the change in the heart shadow due to the descent of the diaphragm was slightly greater than that due to the magnification from the divergence of the rays. For this reason the standard teleroentgenogram is made during quiet respiration. Unfortunately the plates made in four of the cases in 1914-1916 were taken at a thirty-inch distance at full inspiration, the technic used for the study of the lung fields. This study, however, is not concerned so much with the exact size of the heart as with an estimation of the possible changes in its size which might occur during the course of paroxysmal rapid heart action. Therefore, we believe that two plates taken at approximately the same distance at the same period in the respiratory cycle will furnish data sufficiently accurate for this purpose, i. e., the comparison of the relative sizes of the heart shadow in the same patient on two different occasions.

The presence of rotation can very easily be determined by observation of the relation of the shadows of the sternoclavicular joints to that of the spine. Very slight degrees of rotation produce errors which are insignificant and which do not vitiate the observation. In this series it occurred in very few plates and in such slight degrees that it has been ignored.

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4. LeWald, L. T., and Turrell, G. H.: The Aviator's Heart. Roentgen Ray Studies Under Conditions Simulating High Altitudes, Am. J. Roentgenol. **7**:67, 1920.

It is generally accepted that changes in the measurements of the heart shadow up to 0.5 cm. and in the cardiothoracic ratio of 2 per cent. are within the limits of error and may be discounted.

In estimating the change in the heart shadow we have used the actual difference in the transverse diameters and the difference in the cardiothoracic ratios. In a review of Table 1, one is readily impressed by the absence of any distinct dilatation in most of the cases. When it is remembered that changes of 0.5 cm. or less in the transverse diameter of the heart shadow and of 2 per cent. in the cardiothoracic ratio are within the limits of error, there remain only three cases in which an appreciable dilatation of the heart occurred. Case 1 shows the most marked change in the series. Here the heart dilated sufficiently to produce an increase of 2.8 cm. in the transverse diameter and of 14 per cent. in the cardiothoracic ratio. This patient was also seen in a similar attack some months later and a dilatation was again observed with an increase of 2.5 cm. in the heart shadow. Unfortunately, one of these plates was lost. The marked dilatation in this case probably was the result of the extremely rapid heart rate and the comparatively long duration, for nothing abnormal in the heart itself could be detected between attacks. Case 3 was a patient with severe valvular disease who showed clinical evidence of a markedly damaged myocardium. In this case there was an increase of 1 cm. in the transverse diameter and of 4 per cent. in the cardiothoracic ratio. Despite the short duration and the rather low heart rate during tachycardia (162), distinct dilatation occurred and may be explained by the poor condition of the heart that was evident when the rate was normal. Case 8 was an elderly colored man with a severe chronic myocarditis who had attacks of ventricular tachycardia. A roentgenogram taken during an attack, twelve hours after the onset, while the rate was 165, showed an increase of 1.4 cm. in the transverse diameter of the heart shadow and of 5 per cent. in the cardiothoracic ratio over the measurements made after the heart had returned to normal rate. This dilatation may be explained as in the previous case. In seven of the remaining eight cases the changes did not exceed the limit of error. In Case 4 questionable increase in the size of the heart occurred, the cardiothoracic ratio being 3 per cent. larger during than before the attack, and 2 per cent. larger during than after the attack. It is interesting that this patient, who had mitral stenosis, had considerable dilatation of the left auricle during the attack as is shown in Figure 1. In Cases 2 and 11 there was an apparent decrease in the size of the heart shadow during the attack.

The main interest in these roentgen-ray findings is the absence of definite dilatation in the majority of the cases. It is fair to say that, with the exception of Case 1, and possibly of Case 8, it would be impossible

to detect by percussion and palpation any of the changes that occurred in this series. For it must be appreciated that when a change in the transverse diameter of the heart shadow occurs, it may be divided into two portions, one to the right and one to the left of the midline. For example, in Case 3, to detect the difference of 1 cm. that occurred, it would be necessary to percuss an increase of 7 mm. to the right and 3 mm. to the left. It must not be understood that even the slight dilatation that escapes clinical detection is not significant, for if the transverse diameter of the heart increase 0.5 cm. it would mean considerable stretching of the muscle fibers and likewise a considerable increase in the heart volume. But the important point is that the dilatation is so slight in most cases that it cannot be detected on ordinary bedside examination, and that only in isolated cases is it very appreciable even when roentgen-ray examinations are made. It appears to us that the three factors that determine whether dilatation will occur are the duration of the attack, the rapidity of the ventricular rate during the attack and the general health of the heart. The longer the attack, the more rapid the heart rate and the more severely damaged the heart, the more apt it is to dilate.

Observations on the systolic, diastolic and pulse pressures were made on seven of the patients during the course of rapid heart action and again while the heart mechanism was normal. Our interest was aroused by Case 1. The patient, who had suffered serious accidents with three attacks, always showed a remarkably small pulse pressure during those in which he was observed. With such a sluggish circulation, it is not surprising that he developed gangrene of an arm, hemiplegia and aphasia.

In Case 1 (Table 3) the systolic pressure fell and the diastolic rose, resulting in a pulse pressure of 8 mm. as soon as eight hours after the onset of the attack although the patient had no demonstrable heart disease. This occurred because the rate was extremely fast, about 250 to the minute. Case 2, on the other hand, showed a very low pulse pressure of 10 mm. when the attack had lasted three days, but the change was only slight during another attack when the readings were made after it had lasted only sixteen hours. Case 4 illustrates the rapid development of a small pulse pressure, for within fifteen minutes after the onset of a rate of 233 it was only 12 mm., while nine minutes after the attack had ended the pulse pressure had risen to 18 mm. and three hours later to 24 mm. This rapid change took place because of the very fast heart rate and because the patient was already suffering from mitral stenosis. Similarly Case 7 showed a decrease in the pulse pressure from 31 mm. to 18 mm. and from 46 mm. to 14 mm. only a few hours after the onset of two attacks, although the heart rate was only 160. This is explained by the fact

that the patient was already suffering from chronic myocarditis. Likewise in Case 8, a chronic myocarditis, a small pulse pressure developed within one hour after the onset of tachycardia, although the heart rate rose to only 165. The last patient (Case 9), who had aortic stenosis and a low systolic pressure of about 90 mm., when the heart was beating normally, showed a pulse pressure of only 12 mm. three days after the attack of auricular flutter had begun, while the ventricular rate was

TABLE 3.—Blood Pressure Readings

Case	Diagnosis	Date	Heart Rate	Blood Pressure			Time of Blood Pressure Readings in Relation to Attacks
				Systolic	Diastolic	Pulse	
1	Paroxysmal auricular tachycardia	12/28/14	250	94	86	8	2 days after onset
		1/ 3/15	82	100	66	34	3 days after end
		7/14/15	242	84	76	8	8 hours after onset
2	Paroxysmal auricular tachycardia, syphilis (positive Wassermann)	7/ 6/16	217	124	114	10	3 days after onset
		7/ 7/16	80	110	75	35	1 day after end
		7/10/16	86	148	116	32	1 day after end
		7/13/16	192	9.	65	30	16 hours after onset
		7/15/16	68	135	95	40	1 day after end
3	Paroxysmal auricular tachycardia, aortic and mitral insufficiency, chronic myocarditis	12/ 9/16	162	148	30 ?	118	10 hours after onset
		12/13/16	90	300	0 ?	300	1 day after end
4	Paroxysmal auricular tachycardia, mitral stenosis	11/ 5/16	130	120	95	25	2 days before attack
		11/ 7/16	233	136	124	12	15 minutes after onset
		11/ 7/16	233	138	126	12	17 minutes after onset
		11/ 7/16	233	134	122	12	19 minutes after onset
		11/ 7/16	140	126	108	18	9 minutes after end
		11/ 7/16	132	132	108	24	5 hrs. 22 min. after end
7	Paroxysmal ventricular tachycardia, chronic myocarditis	10/25/16	160	98	80	18	? hours after onset
		10/30/16	90	106	72	31	3 days after end
		11/ 3/16	160	97	83	14	Few hours after onset
		11/ 7/16	86	114	68	46	3 days after end
8	Paroxysmal ventricular tachycardia, chronic myocarditis	1/ 3/20	84	145	95	50	1 day before onset
		1/ 4/20	164	115	94	21	1 hour after onset
		1/ 5/20	165	112	94	18	24 hours after onset
		1/ 5/20	168	110	90	20	25 hours after onset
		1/ 8/20	165	110	92	18	12 hours after onset
		1/19/20	82	124	92	32	12 hours after end
9	Paroxysmal auricular flutter, aortic stenosis and insufficiency	2/ 5/15	176	92	80	12	3 days after onset, average of 6 readings
		2/ 6/15	74	90	69	21	6 hours after end, average of 3 readings
	Averages.....	In.....	194.3	112.5	90.4	22.1	
		Out.....	94.2	126.7	81.4	45.1	

176; six hours after the attack had stopped the pulse pressure had risen to 21 mm.

This discussion, although it includes only seven cases with a comparatively small number of blood pressure readings, indicates that during attacks of rapid heart action there is a tendency for the pulse pressure to decrease. The extent of this diminution, like the occurrence of dilatation, will depend on the duration of the attack, the rapidity of the heart and the state of health of the heart muscle. It also shows that the pulse pressure may occasionally become dangerously low when

these three factors are sufficiently antagonistic to an efficient circulation. The figures at the bottom of Table 3 indicate that the decrease in pulse pressure is brought about by a fall in systolic pressure and an increase in diastolic pressure, for although there are some variations in the isolated observations, the average of all readings shows a fall of systolic pressure from 126.7 mm. to 112.5 mm., and a rise of diastolic pressure from 81.4 mm. to 90.4 mm. during attacks. Readings made on other patients with paroxysmal rapid heart action, not included in this study because no roentgen-ray observations were made, showed similar changes.

In addition to the roentgen ray and blood pressure determinations, a study of these cases showed that a leukocytosis and slight fever were not uncommon findings during the attacks of rapid heart action. In some instances they were quite striking, the temperature and leukocyte count falling to normal promptly after the attack was over. Six of the patients had a leukocytosis of from 13,000 to 22,000 during the upsets and two had a temperature of over 100 F. It does not seem likely that an actual infection had taken place which brought on the tachycardia, but rather that the fever and leukocytosis were the result of the cardiac upset.

SUMMARY

Roentgen-ray examinations and blood pressure studies were made on eleven patients with paroxysmal rapid heart action. Five had paroxysmal auricular tachycardia, three had paroxysmal ventricular tachycardia, one had paroxysmal auricular flutter and two had paroxysmal auricular fibrillation. Observations were made during the attacks and while the heart was beating normally.

It was found that in eight cases no appreciable dilatation of the heart occurred, in two it was definite but slight and in one it was considerable. These results indicated that in ten out of eleven cases it would have been impossible to detect with any certainty by percussion and palpation a change in the size of the heart.

In seven of the cases blood pressure readings showed that the systolic pressure was apt to fall and the diastolic pressure to rise, resulting in a low pulse pressure which in rare instances became very small, i. e., 8mm. This low pulse pressure may explain some of the symptoms that occur during the severe attacks.

It is suggested that the amount of dilatation and the decrease in pulse pressure are dependent on three factors; the duration of the attack, the rapidity of the ventricles during the attack and the state of health of the heart before the attack occurs.

In several cases a leukocytosis, even as high as 20,000, and a temperature of 100 F. developed with the attacks and quickly subsided as the heart returned to normal.

REPORT OF CASES

CASE 1 (Med. No. 2092).—*History.*—A baker, age 38, was seen at the hospital on numerous occasions for attacks of palpitation. The first attack occurred about four years before his first admission to the hospital. It lasted four days and during it he suddenly developed loss of memory which lasted for a year. The second attack occurred about one year later and continued for eight and one-half days. During the seventh day he developed a right hemiplegia which cleared up after six months, leaving a slight weakness of that side of the body. Two and a half years before the first admission he had the third attack. This lasted ten days, but on the eighth day he developed dry gangrene of the left arm which required amputation just below the shoulder. Dec. 26, 1914, following a fall downstairs, he noticed his heart beating irregularly and later rapidly. At times there were sharp gripping pains over the heart and a feeling of dizziness. He was short of breath after the onset but had no orthopnea, cough or edema. All the previous attacks began and ended suddenly. He entered the hospital Dec. 28, 1914.

Physical Examination.—This showed a well developed man with a very anxious expression on his face. His skin was covered with a profuse perspiration. Very rapid oscillatory pulsations were seen over the jugular bulbs. Heart examination showed an extremely rapid regular rate, 250 to the minute. No murmurs were heard. The second heart sound could not be heard. Lungs were negative, liver edge not felt, no edema of the legs. The fingers and lips were distinctly cyanosed.

The urine was negative. The blood showed 21,300 leukocytes, with 80 per cent. polymorphonuclears during the attack, and 7,700 two days later during normal rate. The temperature ranged around 101 F. during the attack and then fell to normal. The blood Wassermann was negative. Electrocardiograms taken during the attack showed paroxysmal tachycardia of auricular origin.

Course.—Numerous attempts to stop this attack by ocular and direct vagal pressure were unsuccessful. It stopped spontaneously two and a half days after admission. During the following two years the patient was observed in several similar attacks all of which were successfully ended by pressure over the carotid artery. During one of these further blood counts were made and a leukocytosis of 25,400 was found; there was no fever. The following day when the heart rate was normal the white count was 6,000. Between attacks examination showed the heart to be normal.

Blood pressure readings on the first admission to the hospital were: during tachycardia, systolic, 94; diastolic, 86; five and seven days later during normal rate: systolic, 100; diastolic, 66, and systolic, 114, diastolic, 84, respectively. Several months later during an attack: systolic, 84; diastolic, 76; one-half hour after the attack was ended by vagal pressure: systolic, 106; diastolic, 86. The following morning: systolic, 130; diastolic, 90. Roentgenograms were taken at a distance of about thirty inches during and after two attacks, and showed an increase in the transverse diameter of about an inch while the tachycardia was in progress. During recent years the patient has had occasional attacks which he has been able to stop by vagal pressure or holding a deep inspiration.

Diagnosis.—Paroxysmal auricular tachycardia.

CASE 2 (Med. No. 4940).—*History.*—A woman, 50 years old, entered the hospital June 5, 1916, complaining of palpitation. Twenty-five years previously she had typical rheumatic fever. Thirty-five years previously, while stooping to pick up something from the floor, her heart suddenly began to beat very rapidly. This attack lasted five minutes. Similar attacks recurred every eight or twelve months, gradually becoming more frequent and of longer duration. Things would become black before her eyes at the beginning and end of each attack. She would always lie down during the attacks. The longest attack

was of seven days' duration. Recently she had been having an "aura" of indigestion, a heavy feeling in the abdomen, nausea, gas and nervousness for two or three days ending with precordial pain just preceding the attack. Riding in a buggy on a rough road used to stop the attacks, later running up and down stairs and applying ice to the precordium were successful, but now the only thing that works is vomiting for which she uses ipecac. During the attacks she had dyspnea on slight exertion, a tight sensation in the chest and tremendous palpitation. The upset which brought her to the hospital began June 2, 1916.

Physical Examination.—This showed a somewhat enlarged heart with an extremely rapid and regular rhythm but no murmurs. There was an area of hyperesthesia in the right hypochondrium and a palpable and very tender liver edge. Vagal pressure was tried without success. The attack stopped spontaneously the night following admission, i. e., four days after the onset. During her stay she had several other shorter attacks, some stopping spontaneously while others were ended by vomiting induced by ipecac.

Thee white count was from 18,000 to 21,000. The urine showed a large trace of albumin on admission which later completely disappeared. The phenolsulphonepthalein output in two hours was 48 per cent. Wassermann reaction was strongly positive. The basal metabolism during the attack was + 27 per cent.; during normal rate, + 6 per cent. Electrocardiograms showed paroxysmal tachycardia of auricular origin with a rate of 217.4. There was typical alternation of the ventricular complexes. Blood pressure readings were: during first attack, July 6: systolic, 124; diastolic, 114; July 7, normal rate: systolic, 110; diastolic, 75; July 13, during the third attack (duration one day): systolic, 95; diastolic, 65; two days later with normal rate, systolic, 135, diastolic, 95. Roentgenograms taken at seven feet during and after the attack showed no appreciable change in the transverse diameter of the heart.

Course.—She was discharged July 26 improved.

Diagnosis.—Paroxysmal auricular tachycardia; syphilis (positive Wassermann).

Case 3 (Med. No. 5742).—*History.*—A man, aged 21, entered the hospital Dec. 9, 1916, complaining of pain in the heart and palpitation. He had rheumatic fever in 1913 and was quite sick for four months, after which he had frequent attacks of sore throat. For four years he noticed shortness of breath, and in 1915, after climbing a flight of stairs, he had severe palpitation. He had numerous attacks of palpitation since then, at first coming on about once a month but more recently every day. Generally, the attacks were of short duration, sometimes lasting minutes or a few hours, but one attack continued for twenty-four hours. Patient stated that at the commencement of an attack the heart became irregular, weak beats and forceful thumps interspersed with pauses and then the heart would finally "start its race." At the time of admission and for several days afterward he had frequent short paroxysms of tachycardia causing marked subjective discomfort.

Physical Examination.—This showed an enlarged heart with signs of aortic and mitral insufficiency. There was no congestion of the lungs or edema of the legs. The liver was not enlarged. The pulse rate generally was around 100 or 120, and would suddenly rise to 160 during attacks.

Electrocardiograms showed paroxysmal tachycardia of auricular origin. Pulse tracings showed pulsus alternans during attacks. The urine was negative. Blood Wassermann was negative. There was a leukocytosis varying from 15,400 to 22,400. The temperature was essentially normal throughout. During attacks systolic blood pressure was 148 while at other times it ranged around 200; the diastolic figure could not be obtained. Roentgenograms were taken at a distance of seven feet during and after an attack on December 13. The plate taken during the attack showed the transverse diameter of the heart shadow to be 1 cm. greater than that of the plate taken after the attack.

Course.—During his stay in the hospital the patient was extremely sick, suffering with severe precordial pain, and having frequent paroxysms of tachycardia which were generally stopped by vagal or ocular pressure. One day he had an attack of unconsciousness with gasping respirations. The general condition gave the impression of severe myocardial damage in addition to the valve defects. He gradually improved so that during the last two weeks of his stay in the hospital he was absolutely free from attacks. He was discharged improved Jan. 4, 1917.

Diagnosis.—Aortic and mitral insufficiency; chronic myocarditis, paroxysmal auricular tachycardia.

The patient died about one year later.

CASE 4 (Med. No. 12207).—*History.*—A seamstress, aged 24, came to the hospital Dec. 5, 1919, complaining of "heart spells." She had the ordinary children's diseases, frequent sore throats and typical rheumatic fever lasting one month at the age of 10. One year later, while jumping rope, she suddenly had a queer sensation in her throat "as if her heart had jumped up." She felt faint and found that her heart was beating very rapidly. She remained in bed two weeks, at the end of which time she vomited and the heart slowed down as suddenly as the attack had begun. Following that similar attacks recurred about twice a year, always ending with a vomiting spell which was not voluntarily induced. Later the attacks were much shorter in duration and more frequent, appearing every few weeks and lasting about twelve hours; generally the heart rate was around 200. She thought that her upsets were brought on by dietary indiscretions, excitement or exertion.

Physical Examination.—At the time of admission the patient was not having an attack, but came in to be studied. She had typical signs of mitral stenosis, with a pulse rate of 120, but without evidence of decompensation. Otherwise the physical examination was negative.

The urine and blood Wassermann were negative. White blood count on admission was 13,200.

Course.—Two days after admission the patient developed one of her attacks of rapid heart action, the rate jumping from 90 to 233. Electrocardiograms confirmed the diagnosis of paroxysmal auricular tachycardia. After numerous attempts to stop the attack by having the patient hold a forced inspiration and by pressure over the eyeballs and over the carotids, left vagal pressure finally ended the attack, the heart rate returning to its previous level. Blood pressure readings were made as follows: before the attack: systolic, 120, diastolic, 95; during the attack: systolic, 136, diastolic, 124; nine minutes after the attack: systolic, 126; diastolic, 108; three hours later: systolic, 132; diastolic, 108; five days later: systolic, 125; diastolic, 85. Roentgenograms were taken before, during and after the attack, and showed a definite dilatation of the left auricle during the paroxysm but no appreciable increase in the transverse diameter of the heart shadow. She had no further attacks in the hospital and was discharged on Nov. 15.

Diagnosis.—Mitral stenosis, rheumatic in origin, paroxysmal auricular tachycardia.

CASE 5 (Med. No. 13577).—*History.*—A woman, aged 50, entered the hospital, May 18, 1920, complaining of painful swelling of the hands and feet. Seven weeks before admission she suddenly noticed painless swelling of the sole of the left foot. Three weeks later a similar swelling appeared in the right foot. Each lasted about a week. In the meantime, the joints of both hands and feet began to ache and swell.

Course.—During her stay of four months in the hospital she ran a typical course of chronic infectious arthritis. Blood pressure on admsision was: systolic, 180; diastolic, 115. At times she had a fever, and her urine showed many pus cells which were thought to be due to a pyelitis. The leukocyte count, except on one occasion, was normal. Blood Wassermann was negative.

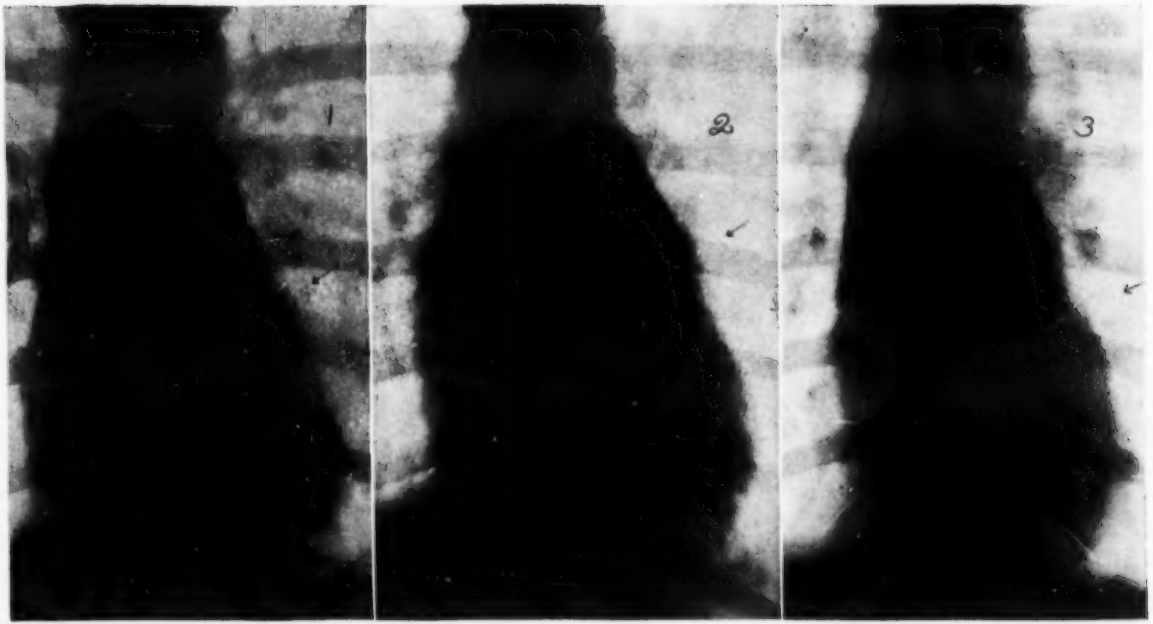

Fig. 1.—"Seven-foot" roentgenograms taken in Case 4 (paroxysmal auricular tachycardia; mitral stenosis) (1) November 6 before; (2) November 7 during, and (3) November 10 after the attack. Arrow points to left auricle. Note prominence of auricular shadow during attack. No appreciable increase in transverse diameter of heart shadow.

Incidental to her main illness, on two days she had transient attacks of tachycardia lasting a few hours. These caused no inconvenience to the patient, and in fact were discovered on routine examination. During the attacks the heart rate was 175 to 180. One was observed to end spontaneously and the other was stopped by vagal pressure. No observations on blood pressure or leukocyte counts were made during these attacks. Electrocardiograms showed paroxysmal auricular tachycardia. Pulse tracings during the attacks showed pulsus alternans. Examination of the heart during the slow rate showed definite enlargement. Roentgenograms taken at seven feet during and after one of the paroxysms showed no change in the size of the heart. She was discharged Sept. 19, 1920, with her joint condition unimproved.

Diagnosis.—Chronic infectious arthritis; paroxysmal auricular tachycardia.

CASE 6 (Med. No. 3324).—*History.*—A woman, age 64, entered the hospital Sept. 10, 1915, complaining of palpitation. Her father died at 51 of apoplexy. Her mother died suddenly at 34 presumably of heart disease. Two brothers died of heart disease (one suddenly). Patient had been a school teacher for forty years and had never missed a day's work until the week before admission. During April, 1915, she began to have palpitation and oppression in the chest. She kept at work but often had to lie down during attacks of palpitation. For a year she noticed slight shortness of breath and swelling of the ankles at night. For three months walking would bring on a feeling of faintness and palpitation. She took tincture of digitalis and some strychin off and on during the month before admission. The morning of entry to the hospital she awoke with a sense of oppression in the chest and a rapid heart.

Physical Examination.—Negative, except for rapid heart action and poor heart sounds. The rate was 160 per minute and regular. Electrocardiograms showed paroxysmal tachycardia of ventricular origin. After the resumption of the normal rate the heart examination was also negative.

The urine and the leukocyte count were essentially normal. The blood Wassermann was negative. Temperature remained normal throughout.

Course.—The patient had numerous attacks of tachycardia lasting from a few minutes to several hours, and although frequent attempts were made to stop the attacks by ocular and vagal pressure none were successful. In addition there were times when the heart mechanism showed transient auricular fibrillation. The admission blood pressure, which was the only one obtained, was: systolic, 116; diastolic, 70. Roentgenograms taken at a distance of about thirty inches during tachycardia and during normal rate showed no appreciable change in the size or outline of the heart. She gradually improved with rest in bed and small doses of digitalis and was finally discharged Dec. 16, 1915, improved.

Diagnosis.—Chronic myocarditis; paroxysmal ventricular tachycardia.

Patient died suddenly Oct. 1, 1916.

CASE 7 (Med. No. 5503) *History.*—A machinist, 50 years old, entered the hospital Oct. 25, 1916, complaining of indigestion and palpitation. He had consumed large amounts of tobacco and was a moderate drinker. One year previously he had an attack of indigestion lasting ten days. He belched a great deal of gas, vomited after meals and was constipated. During this time he had dull pains down both arms, palpitation and rapid heart. One and a half months before admission he had a similar attack. Since then attacks of palpitation have been the most troublesome complaint. A few days before entering the hospital he thought he was going to die during an attack. These attacks lasted about fifteen minutes and occurred daily for three weeks. For one month he had increasing dyspnea and orthopnea. There was no edema, cough or precordial pain. For a few days he had dizzy spells requiring him to hold on to nearby objects for support.

Physical Examination.—This showed a very sick-looking, orthopneic man, with a pasty yellowish appearance to his face. The lips were cyanosed. The

heart was considerably enlarged, the sounds distant, rapid and regular, rate 160, and no murmurs. The lungs were negative. The liver edge was felt 4 cm. below the costal margin and was tender. There was slight edema of the ankles.

The urine showed a very slight trace of albumin and a few granular casts. Subsequently the urine became normal. There was a leukocytosis of 19,000. The Wassermann reaction was negative. There was a temperature of about 100 F. for a few days. Electrocardiograms taken during the attack showed paroxysmal ventricular tachycardia.

Course.—The attack which brought the patient to the hospital continued for about three days. Numerous attempts at vagal and ocular pressure failed to produce any slowing of the heart rate. Three grams of digitalis leaves were given during the course of the first eight days in the hospital. Shortly before the attack ended the patient had a spell of hiccoughing. During the second week in the hospital he had another attack lasting about twenty-four hours. Blood pressure readings were made at various intervals during and after attacks. October 25, the heart rate was 160; systolic pressure, 98; diastolic, 80. October 30, with the heart rate normal, systolic pressure was 103; diastolic, 72. November 3, the heart rate was 160; systolic pressure, 97; diastolic, 83. November 7, with a normal heart rate, systolic pressure was 114; diastolic, 68. Roentgenograms taken at a distance of about thirty inches during and after the second attack showed no appreciable change in the shape or in the transverse diameter of the heart. Discharged November 16, improved.

Diagnosis.—Chronic myocarditis; paroxysmal ventricular tachycardia.

CASE 8 (Med. No. 12646).—*History.*—A colored man, aged 64, entered the hospital Jan. 3, 1920, complaining of dizziness. During the previous year he had five or six spells of dizziness and fainting, in which he fell to the ground and lost consciousness for five or ten minutes. After this he felt weak and unsteady. For the previous five or six weeks he had shooting pains in his legs, and for one week there was increasing dyspnea and weakness so that he was compelled to remain in bed.

Physical Examination.—This showed cyanosis of the lips and finger tips. The heart was considerably enlarged and there was a blowing systolic murmur at the apex. The heart rate on admission was 90. There was some congestion at the base of the left lung. The liver edge was just felt below the right costal margin. There was no edema of the legs.

The urine on admission showed a trace of albumin which cleared up subsequently. There were no casts. The leukocyte count on admission was 13,600; the temperature was 99.6 F. The Wassermann reaction was negative.

Course.—The day after entry his heart rate jumped from 74 to 160 and electrocardiograms showed paroxysmal tachycardia of ventricular origin. Pulse tracings at this time showed pulsus alternans. This attack lasted thirty hours. During his stay in the hospital he had several such attacks lasting generally two hours. Numerous attempts to stop the paroxysms by ocular and vagal pressure were unsuccessful; they always ended spontaneously. The blood pressure on admission with a normal heart rate was: systolic, 145; diastolic, 95. The next day during tachycardia it was: systolic, 115; diastolic, 94. On two other days during tachycardia three readings were obtained as follows: (1) systolic, 112; diastolic, 94; (2) systolic, 110; diastolic, 90; (3) systolic, 110; diastolic, 92. Jan. 19, 1920, during normal heart rate, the readings were: systolic, 124; diastolic, 92. Roentgenograms were taken at a seven-foot distance during and after one attack. The transverse diameter of the heart shadow was slightly but definitely increased during the attack.

Course.—During the first two weeks, the patient was dangerously ill, but with rest in bed and digitalis therapy he gradually improved and became free from attacks. He was discharged March 10, 1920, improved.

Diagnosis: Chronic myocarditis; paroxysmal ventricular tachycardia.

CASE 9. (Med. No. 1791).—*History.*—A man, age 35, entered the hospital Oct. 21, 1914, complaining of shortness of breath. Two years previously he had an attack of acute tonsillitis with some stiffness of the elbows. On October 9 he began to have pain in his shoulders and arms and on the following day he felt that his heart was beating rapidly. He kept about his work but on the sixteenth he began to feel short of breath. After staying two days in the hospital the patient was displeased with his treatment and left. His course, however, was followed in the Outpatient Department from time to time. The attack of rapid heart action and shortness of breath ended some time between October 22 and 29. After this he was well for three weeks when a similar attack occurred lasting three weeks. He remained in good health until Feb. 2, 1915, when the third attack began, associated with pain in the left ankle and both shoulders.

Physical Examination.—During the two attacks which were observed the physical findings were essentially the same. The heart was definitely enlarged and the action rapid and regular, 176 to the minute. No murmurs were heard. There were prominent pulsations in the veins of the neck. During the first attack the urine was negative, the white count was normal, the temperature was 99.2 F. and the blood Wassermann was negative. During the second attack the temperature was 99.4 F. At this time he was given 1 gm. sodium salicylate, every three hours, and digitalis leaves, 0.1 gm., three times a day. Electrocardiograms taken during both attacks showed that the auricles were fluttering with a rate of about 350 and the ventricles were contracting regularly to every other auricular impulse. February 6 he awoke and found that his heart was beating normally. Examination during this normal rhythm disclosed signs of aortic stenosis and slight aortic insufficiency, i. e., there was a prominent systolic thrill in the aortic area, a loud systolic murmur and a faint but definite diastolic murmur. The blood pressure February 2, during an attack, was systolic, 92; diastolic, 80; February 6, during normal rate: systolic, 90; diastolic, 69. Roentgenograms taken at about thirty inches during and after both the first and third attacks showed no appreciable change in the outline or in the transverse diameter of the heart shadow. The first plate was taken when the attack had lasted twelve days. The roentgenogram during the other attack was taken when it had been in progress three days.

Course.—The patient returned to Bulgaria, his native country, and was reported to have joined the army and to have died during the succeeding year or so.

Diagnosis.—Aortic stenosis, slight aortic insufficiency; paroxysmal auricular flutter.

CASE 10 (Med. No. 13074).—*History.*—A woman, aged 38, entered the hospital March 2, 1920, complaining of pain in the heart and stomach. Following curettage two years previously she developed precordial pain and palpitation. This passed away and she had no further trouble until five weeks before admission when she began to have severe epigastric and precordial pain, palpitation, nocturnal dyspnea and orthopnea.

Physical Examination.—This showed an enlarged heart with an absolutely irregular rhythm and a loud blowing systolic murmur at the apex. There was a pulse deficit of 20 beats. A tender liver edge was felt. There was no edema of the legs.

The urine on admission showed a trace of albumin which cleared up subsequently. The leukocyte count was normal. The Wassermann reaction was negative. The basal metabolism was plus 39 per cent. The temperature was normal throughout. The day following admission the cardiac rhythm became regular.

Course.—During her stay in the hospital she had several attacks of paroxysmal auricular fibrillation, which diagnosis was confirmed by electrocardiograms.

Roentgenograms were taken at a distance of seven feet during and after an attack of fibrillation and showed no definite change in the size or contour of the heart shadow. There was evidence of cardiac hypertrophy. The patient improved slowly with rest in bed and with digitalis. She impressed some of those who saw her as suffering from hyperthyroidism and others thought she had mitral stenosis. She was discharged May 17, 1920, improved.

Diagnosis.—Mitral stenosis and regurgitation; paroxysmal auricular fibrillation.

Case 11.—*History.*—A man, aged 26, came to Dr. Paul D. White at the Massachusetts General Hospital Dec. 14, 1920, complaining of palpitation. The first attack occurred during the spring of 1916 while he was playing tennis. For one hour his heart beat very tumultuously, rapidly and irregularly. Two or three months later there was a second attack. He had numerous similar attacks after this and the usual interval between them was two or three months, except while he was driving a motor cycle in France, when they came weekly. He was sent home as a case of effort syndrome. These upsets started and stopped suddenly and lasted from one hour to more than a day. During the attack he had slight dyspnea, weakness and marked palpitation, but he never had to stop work.

Physical Examination.—The attack which brought him to Dr. White began the previous day about 11 p. m. Electrocardiograms showed auricular fibrillation with a ventricular rate of from 110 to 130.

Course.—No effect was produced by right or left vagal or right ocular pressure. December 16 he was seen again after the attack had stopped. Examination of the heart disclosed no evidence of valvular disease. Roentgenograms were taken at a distance of seven feet during and after the attack and showed no appreciable change, although there was evidence of hypertrophy.

Diagnosis.—Paroxysmal auricular fibrillation.

A STUDY IN EXPERIMENTAL DIABETES

THE EFFECT OF INTRAVENOUS INJECTION OF PANCREATIC PERFUSATES ON THE D/N RATIO FOLLOWING PANCREATECTOMY *

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The relation of the pancreas to diabetes mellitus was proved in 1889 when Von Mering and Minkowski discovered that fatal diabetes always followed complete pancreatectomy. Two principal hypotheses have been advanced to explain how the pancreas is linked with carbohydrate metabolism, viz., the detoxication and the internal secretion theories. In the former the pancreas is supposed to remove a toxic substance from the blood stream, the presence of which interferes with the oxidation of carbohydrates by the tissues; in the latter the pancreas is said to contribute something to the blood stream which acts as a necessary link in the process of carbohydrate assimilation. Attempts to establish either of these theories have met with little success although the preponderance of evidence to date seems to favor the theory of an internal secretion. Notwithstanding a vast amount of experimentation the exact role of the pancreas in carbohydrate metabolism remains unknown.

The parabiosis experiments by Forschbach,[1] the transplantation and cross circulation experiments by Hedon,[2] pancreas feeding experiments and many others have yielded results either negative or else contributory alike to the detoxication and the internal secretion theories.

The blood transfusion experiments by Carlson and Ginsberg;[3] and by Drennan; the study of experimental diabetes in pregnant dogs by Carlson [4] and the experiments by Clark [5] in which the surviving mammalian heart and pancreas were perfused in circuit, all support the theory of an internal secretion. These conclusions are also supported by the in vitro studies carried out by Cohnheim [6] and Levene.[7]

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* From the Hull Laboratories of Physiological Chemistry and Pharmacology, University of Chicago.

1. Forschbach: Arch. f. exper. Path. u. Pharm. **9**:131, 1908.
2. Hedon: Arch. intern. di. Physiol. **13**:4, p. 255, 1913.
3. Carlson and Ginsberg: Am. J. Physiol. **36**:280, 1915.
4. Carlson: Am. J. Physiol. **28**:391, 1911.
5. Clark, A. H.: J. Exper. Med. **24**:621, 1916.
6. Cohnheim: Ztschr. f. Physiol. Chem. **39**:, 1903.
7. Levene, P. A., and Meyer, G. M.: J. Biol. Chem., 1911.

Of these methods of attack, perfusion experiments seem most promising, for if it can be shown that the pancreas contributes something to a physiologically inert solution passing through its vessels by which utilization of sugar by the tissues is augmented, the theory of an internal secretion would be made tenable. Besides the perfusion experiments of Clark already mentioned, only two references to the direct perfusion of the pancreas could be found. Hustin perfused the pancreas in a study of its external secretion and de Meyer found that by adding a solution previously perfused through a pancreas to one subsequently perfused through a liver there was an increase in liver glycogen.

In the experiments reported herewith an attempt has been made to determine the effect of pancreatic perfusates upon dextrose utilization in depancreatized dogs.

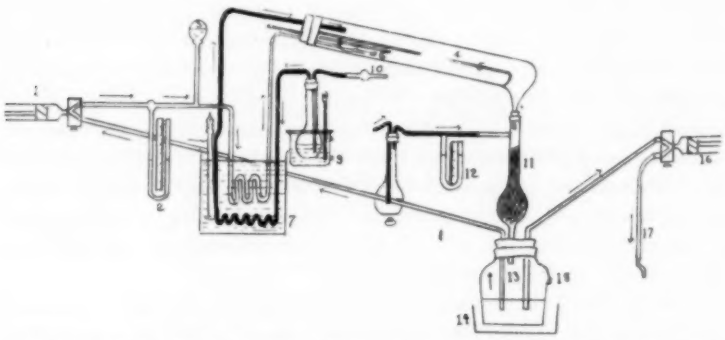

Fig. 1.—1. Woodyatt pump. 2. Mercury manometer for measuring the pressure of the perfusate. 3. Air cushion. 4. Perfusion chamber. 5. Supporting rod to which the pancreas is fastened. 6. Cannula for the pancreaticoduodenal artery. 7. Water bath maintained at 42 C. 8. Water bottle for saturating air with moisture. 9. Bath for maintaining second water bottle at 75 C. In this way the air entering the chamber was heated to from 30 to 35 C. 10. Cotton filter for air entering apparatus. 11. Artificial lung composed of glass beads. 12. Small manometer for registering negative pressure in perfusion chamber. 13. Receiving bottle containing 150 c.c. of perfusion medium. 14. Vessel containing warm water used to warm the perfusate to body temperature previous to injection. 15. Attachment for vacuum pump. 16. Woodyatt pump by which perfusate was injected. 17. Cannula for the saphenous vein. The black tubing carries air.

Method of Procedure.—The D/N ratio was taken as a criterion for the carbohydrate consuming power of the animal. Dogs were depancreatized and the D/N ratios were determined daily. When these figures became rather constant for each animal, it was the plan to inject intravenously a quantity of pure dextrose dissolved in Tyrode's solution. Subsequent determinations of the D/N ratio

should show the amount of dextrose retained after such injections. It was then proposed to perfuse the pancreas of a normal animal with Tyrode's solution containing dextrose, and to inject this perfusate intravenously, at the same rate, into an experimentally diabetic animal, with the expectation that the subsequent D/N ratios would show some change in dextrose utilization.

Females under morphin-ether anesthesia were used for removal of the pancreas. The technic of pancreatectomy was developed so that the complete extirpation of the gland could be assured. Asepsis was given particular attention. The postoperative recovery of the animals was satisfactory and they survived from five days to five weeks.

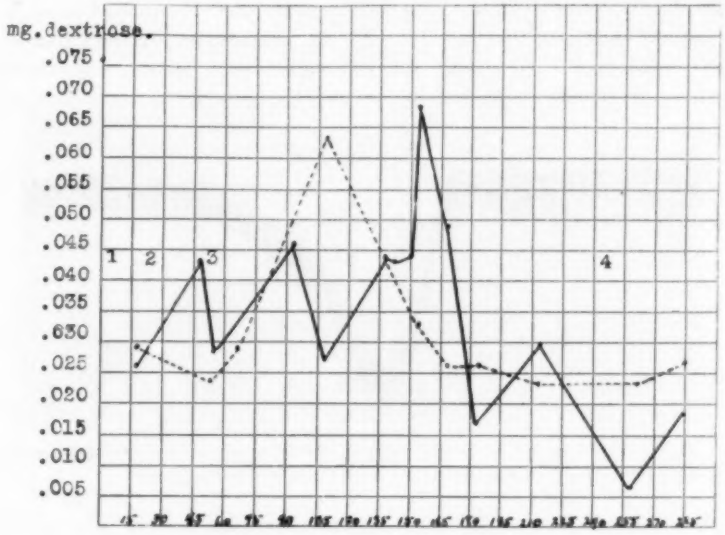

Fig. 2.—Showing the effect on the sugar and nitrogen excretions of repeated injections of pancreatic perfusates. Black line indicates dextrose. Dotted line indicates nitrogen. Figures represent time of injection of perfusate.

Immediately following pancreatectomy the animals were placed in clean metabolism cages and the urine was collected every twenty-four hours. The dogs were kept on a constant daily diet of 480 gm. raw lean meat. Water was given freely. The urine was collected at the same time every day, alcoholic thymol being used as a preservative. The volume was measured and the sugar and nitrogen determinations were made. The total nitrogen was determined by the Kjeldahl-

Gunning procedure. The Munson-Walker-Bertrand method was used for the determination of the urine sugars.

The perfusion medium used in all experiments was Tyrode's solution modified so that it contained no dextrose. The formula was as follows: Sodium chlorid, 0.7 per cent.; potassium chlorid, 0.02 per cent.; magnesium chlorid, 0.02 per cent.; calcium chlorid, 0.02 per cent.; sodium bicarbonate, 0.01 per cent., and monobasic sodium phosphate, 0.005 per cent. Fresh solutions were always used.

The pancreas was perfused as follows: The peritoneal cavity of a dog under morphin-ether anesthesia was opened aseptically by a right rectus incision so as to expose the pancreas. The superior pancreatico-duodenal artery and vein were isolated and ligated close to the origin of the former. The vessels were then cannulated so as to send the perfusion medium through the pancreas in the direction of the blood flow. To render the subsequent steps of the experiment practically bloodless, the thorax was rapidly opened, the aorta clamped

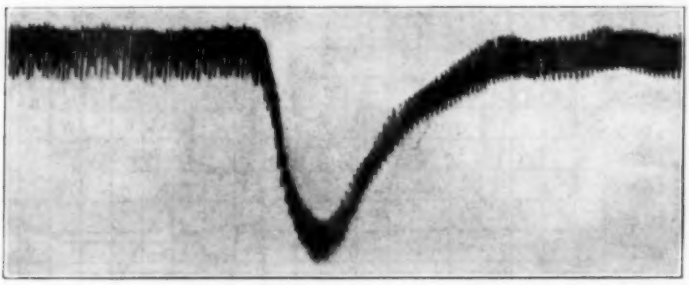

Fig. 3.—Showing effect of the intravenous injection of 1 c.c. of the freshly prepared perfusate on the blood pressure of an etherized animal.

above the diaphragm and the chest cavity quickly closed. The apparatus for maintaining the circulation through the gland was designed so that it could be sterilized in an autoclave. It consisted of a motor driven syringe (Woodyatt transfusion pump) connected through a manometer to the cannula in the pancreatico-duodenal artery. The solution as it came from the pancreatico-duodenal vein poured over glass beads through which a current of moist air was being drawn. The perfusate then flowed into a closed bottle from which it was drawn by the syringe and again sent through the gland. During the procedure the dog was kept under light anesthesia. The perfusate was maintained at 37 C. and a pressure of 120 mm. of mercury. The gland at first became mottled and later white in color as the perfusate continued to pass through its vessels. After fifteen or

twenty minutes moisture was noticed, due to the escape of the perfusate from the surface of the pancreas, and in this way a few cubic centimeters of the solution were lost. By the addition of small quantities of Tyrode's solution at intervals to compensate for this loss on the surface of the gland, a continuous flow of Tyrode's solution through the vessels could be maintained indefinitely.

One hundred and fifty cubic centimeters of Tyrode's solution containing 10 gm. dextrose was allowed to pass through the gland for one hour. At the end of this period a small sample was withdrawn for analysis and the remaining portion injected by means of a Woodyatt apparatus at the rate of 10 c.c. per minute, directly into the saphenous vein of a diabetic animal. Local anesthesia was used to cannulate the vein. The concentration of dextrose in the perfusate was determined in the sample withdrawn for that purpose, and the

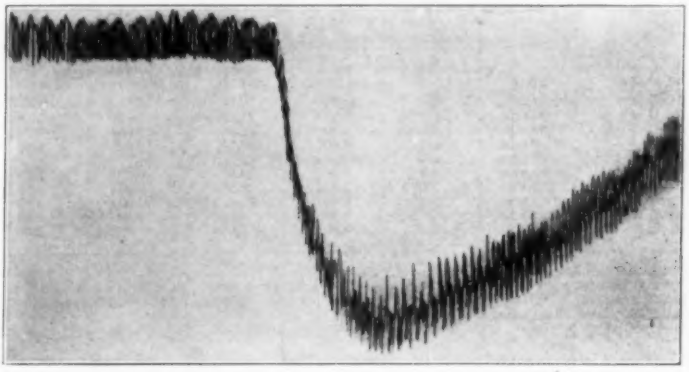

Fig. 4.—Showing effect of the intravenous injection of 1 c.c. of the perfusate allowed to stand for forty hours at room temperature on the blood pressure of an etherized animal.

quantity of sugar injected into the diabetic animal calculated. It was the plan that dogs so treated should show a fairly constant D/N ratio for a period of at least three days preceding the injection. Also the quantity of sugar excreted in the urine following injections of known quantities of pure dextrose was to be determined before injection with the perfusate containing dextrose. It was thought that the pancreatic factor found present by Clark in his perfusates might enable the diabetic animal to utilize all or a portion of the injected dextrose.

Such experiments were attempted on a series of about fifteen depancreatized dogs. Necropsy on these animals revealed complete

removal of the pancreas in almost every instance. Death in a large percentage of cases was caused by pneumonia. Table 1 shows that Dog 8 was injected with 3.27 gm. pure dextrose seventeen days following pancreatectomy. For some unknown reason the daily sugar excretion, preceding the day the animal was injected, rose from 10.54 gm. to 20.35 gm. The following day only 15.15 gm. sugar were excreted in spite of the injection of 3.27 gm. dextrose. In no instance did we feel justified in drawing conclusions as to dextrose utilization from such fluctuating figures.

Having found this procedure useless in the solution of the problem, it was decided to attempt to influence the onset and course of experimental diabetes by the intravenous injection of pancreatic perfusates alone. Such an experiment, if successful, might also throw some light on the hypothetical internal secretion of the pancreas.

TABLE 1.—Experimental Results from Observation of Dog 8, Receiving 480 Gm. Raw Meat per Day. Plenty of Water

Date*	Time	Amount of Urine	Sugar, per Cent.	Sugar Total	Total Nitrogen	D/N
April 3	10:00 a.m.	350	4.70	16.15	.....	....
April 4	10:00 a.m.	470	2.30	11.28	6.063	1.86
April 5	10:00 a.m.	490	2.40	11.76	11.270	1.05
April 6	10:00 a.m.	527	2.00	10.54	12.648	0.83
April 7	10:00 a.m.	260	Contaminated urine			
April 8†	10:00 a.m.	370	5.50	20.35	9.250	2.20
April 9	10:00 a.m.	500	3.00	15.15	9.595	1.58
April 10	10:00 a.m.	265	4.80	12.72	7.950	1.60
April 11	10:00 a.m.	200	4.80	9.60	6.000	1.60
April 12	10:00 a.m.	185	4.60	7.79	7.326	1.06

* Complete pancreatectomy March 22.
† Intravenous injection at 3:00 p. m. of 3.27 gm. pure dextrose dissolved in 100 c.c. of Tyrode's solution. Fifteen minutes was required for the injection. The saphenous vein was cannulated under local anesthesia.

Clarke's work as previously quoted, indicates the existence of such secretion in pancreatic perfusates.

The first line of experiments were conducted as follows: Proceeding on the theory that the animal would most likely respond to treatment while the cells were in a normal physiologic state rather than after they became altered by an abnormal carbohydrate metabolism, intravenous injections of pancreatic perfusates were made immediately following pancreatectomy. In this way the onset of experimental diabetes might be delayed.

The following technic was used in preparing these perfusates. The abdomen was opened by an upper right rectus incision. The splenic end of the pancreas was first liberated as far as the pylorus. The duodenal end was then cut from the mesentery up to the point of its attachment to the bowel wall. The superior pancreatico-duodenal artery was isolated and ligated close to its origin. The thorax was opened and the aorta clamped immediately above the diaphragm so

as to make the subsequent steps practically bloodless. The gland with the attached piece of duodenum, 8 cm. in length, was quickly extirpated and washed in a warm, glucose-free, Tyrode's solution. The pancreatico-duodenal artery was then cannulated and the gland suspended by passing the supporting rod of the perfusion chamber through the lumen of the attached bowel. The splenic end of the pancreas was then tied by a thread to a loop in the supporting rod, and the gland placed in the perfusion chamber. The cannula was connected and the perfusion started. This procedure was carried out in from five to seven minutes. A pressure not to exceed 120 mm. of mercury was maintained and about 15 c.c. fluid was passed through the gland per minute. The perfusate was maintained at 37 C.

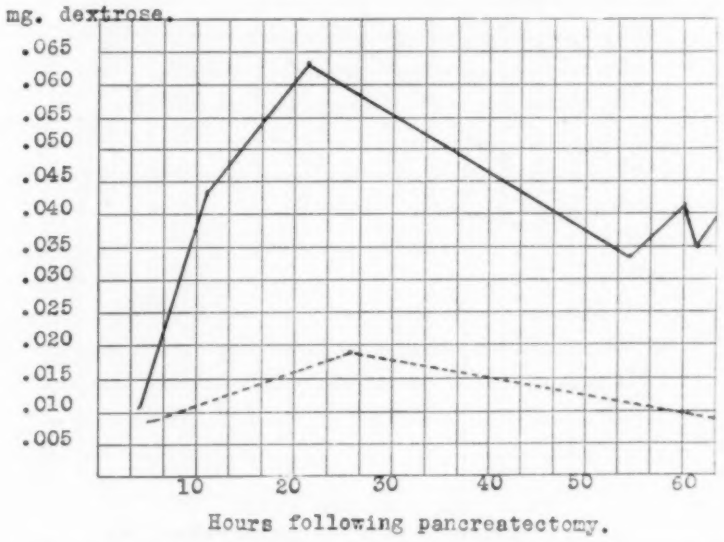

Fig. 5.—Curve showing dextrose and nitrogen excretion for a period of sixty-two hours following the injection of 175 c.c. pancreatic perfusate. The perfusate was prepared by allowing the solution to flow through the gland once. It was injected immediately into the animal following pancreatectomy. Solid lines indicates dextrose. Broken line indicates nitrogen.

For these experiments a special effort was made to devise a perfusion apparatus which would approximate, as nearly as possible, physiologic conditions. A diagram of this is shown and explained in Figure 1. Following each experiment the apparatus was carefully washed and filled with 75 per cent. alcohol. Immediately preceding each experiment the alcohol was removed and repeated washings of Tyrode's solution were pumped through the system. One hundred

and fifty cubic centimeters of fresh, glucose-free Tyrode's solution were then placed in the receiving bottle.

Twenty-seven dogs were used in this series of experiments. None of the animals were fed after operation. The perfusate was allowed to pass through the vessels of the pancreas for one hour. Small, white areas appeared on the surface of the gland almost immediately after the perfusion fluid had entered its vessels. These regions gradually enlarged as the perfusion proceeded until the body and head of the pancreas became white. Aside from this whiteness, due to the washing out of the blood, the tissue remained entirely normal in gross

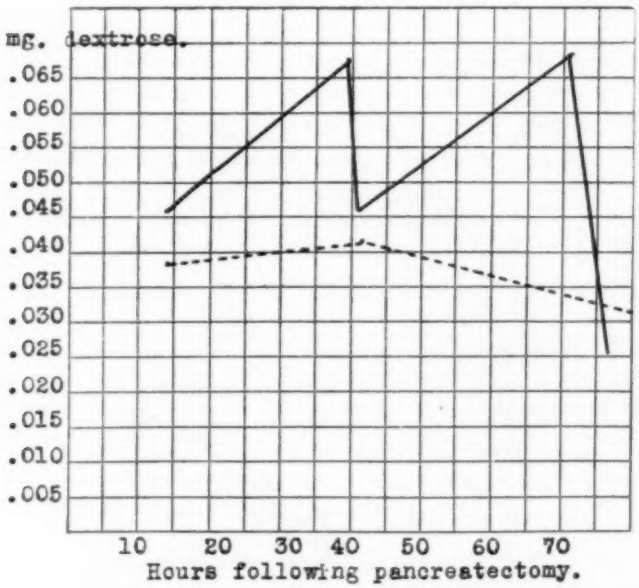

Fig. 6.—Curve showing dextrose and nitrogen excretion for a period of seventy-six hours following injection of 100 c.c. pancreatic perfusate, prepared as described below. Solid line indicates dextrose. Dotted line indicates nitrogen. The perfusate was prepared by passing once through a pancreas 100 c.c. of defibrinated blood drawn from a diabetic dog. It was injected intravenously into a second animal immediately following pancreatectomy.

appearance. Peristaltic waves were often observed traveling along the attached bowel, and these persisted throughout the time of perfusion. While the gland was being perfused, a pancreatectomy was completed. The perfusate was then injected, intravenously, into the depancreatized dog by the Woodyatt apparatus at the rate of 10 c.c. per minute. This operation was done aseptically while the dog was still under ether

anesthesia. Following this the animal was at once placed in a metabolism cage and the urine collected as soon as possible after being voided. The time of the appearance of glycosuria was noted and quantitative sugar and nitrogen determinations were made from this point until the death of the animal.

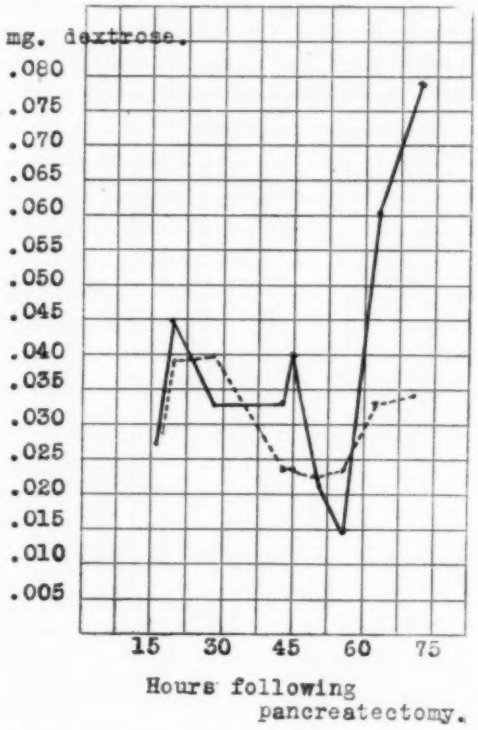

Fig. 7.—Curve showing the dextrose and nitrogen excretion for a period of ninety-two hours following injection with 150 c.c. pancreatic perfusate. The perfusate was allowed to circulate through the gland for one hour and injected immediately following the completion of pancreatectomy. Solid line indicates dextrose. Dotted line indicates nitrogen.

It was found that the course of diabetes following complete removal of the pancreas was fairly constant. Sugar invariably appeared in the urine from six to eighteen hours after complete pancreatectomy and reached its maximum (from 5 to 8 per cent.) in from twenty-four to forty-eight hours. Aside from the glycosuria, the usual diabetic syndrome was noted, viz.: excessive thirst, polyphagia, polyuria, failure of wounds to heal, rapid loss of weight, progressive weakness, and death from complications or extreme inanition.[8]

8. Drennan, F. M.: Am. J. Physiol. **28**:396, 1911.

Dogs injected immediately following pancreatectomy with 150 c.c. of perfusate prepared as described, showed no delay in the onset of glycosuria. There were, however, two exceptions in which sugar did not appear in the urine of animals so injected until forty and fifty-eight hours, respectively, following complete removal of the pancreas. Glycosuria, on appearing, followed its usual course until a few days later when the dogs died of pneumonia. Necropsy on these animals revealed the duodenum to be smooth and free from bits of pancreas visible to the naked eye. Both dogs were in early pregnancy, fetuses measuring from 1 to 1.5 cm. being found.

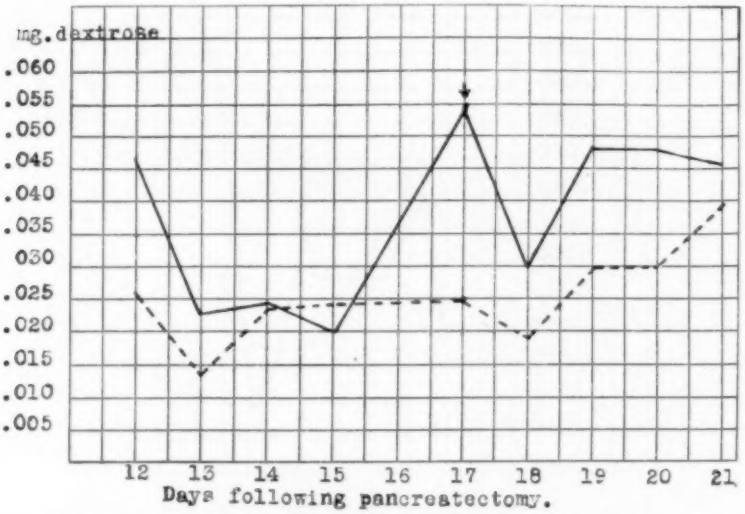

Fig. 8.—Showing glucose and nitrogen output per twenty-four hours on a constant protein diet. Solid line indicates dextrose. Dotted line indicates nitrogen. Arrow indicates intravenous injection of 3.27 gm. pure dextrose.

Glycosuria developed within from six to eighteen hours following pancreatectomy in the remaining ten dogs of this series. As is noticed in Table 2, subsequent injections after glycosuria had developed produced no consistent change in the D/N ratio. Figure 2 shows that the urine sugar did not reach its maximum until 158 hours following pancreatectomy. During this period the dog was injected three times with pancreatic perfusates. The result is typical of those obtained in this series. The delayed sugar excretion is probably apparent rather than real, since it is always followed by a compensatory rise lasting through a period of several hours. The total quantity of glucose excreted for the given period remains unchanged.

This interpretation seems justified by examination of the tracing (Fig. 3) which shows the action of these perfusates on the blood pressure of an etherized animal. Their marked vasodilator effect indicates that they are in this respect similar to tissue extracts. It is known that a fall in blood pressure resulting from the injection of tissue extracts into experimentally diabetic animals is usually accompanied by a decrease in glycosuria followed by a compensatory rise.

TABLE 2.—EXPERIMENTAL RESULTS FROM OBSERVATION OF DOG 20*

Date	Time	Amount of Urine	Sugar, per Cent.	Sugar, Gm.	Total Sugar	Nitrogen, Gm.	Total Nitrogen	D/N
July 6- 7†	9:00 a.m.	175	2.61	4.568	4.568	5.0225	5.0225	0 91
July 7- 8‡	8:45 a.m.	170	4.29	7.293	.....	4.875	.....	....
	12:55 p.m.	90	2.83	0.849	8.142	0.843	5.718	1.42
July 8- 9	8:50 a.m.	75	3.31	2.483	2.483	2.160	2.160	1.15
July 9-10	10:45 p.m.	118	4.64	5.475	.....	7.434	.....	....
	6:00 p.m.	50	2.74	1.370	6.845	3.150	10.584	0.65
July 10-11	No urine							
July 11-12	8:35 a.m.	65	4.42	2.873	.....	2.152	.....	....
	11:00 a.m.	105	4.33	4.547	.....	3.476	.....	....
	7:45 p.m.	85	4.42	3.757	.....	2.814	.....	....
	9:00 p.m.	50	6.72	3.360	14.537	1.655	10.007	1.44
July 12-13	7:30 a.m.	80	4.80	3.84	3.84	2,176	2.176	1.77
July 13-14	8:00 a.m.	65	1.60	1.040	1.040	1.768	1.768	0.62
July 14-15	12:00 n.	215	2.96	6.364	6.364	5.354	3.354	1.89
July 15-16	5:00 p.m.	180	1.60	2.880	2.880	4.446	4.446	0.64
July 16-17§	8:00 a.m.	85	0.70	0.595	0.595	1.394	1.394	0.43
July 17-18	10:00 a.m.	70	1.91	1.337	1.337	1.890	1.890	0.71

* Pancreatectomy complete 12:45 p. m. July 5, 1919. Injected immediately following pancreatectomy with 150 c.c. pancreatic perfusate prepared as described.
† Second injection 12:30 p. m. July 6.
‡ Third injection 12:45 p. m. July 7.
§ Fourth injection 9:00 p. m. July 16.

TABLE 3.—EXPERIMENTAL RESULTS FROM OBSERVATION OF DOG 26*

Date	Time	Amount of Urine	Sugar, per Cent.	Sugar, Gm.	Total Sugar	Total Nitrogen	D/N
July 17	10:00 p.m.	450	1.30	5.806	5.806	4.158	1.42
July 18	7:10 a.m.	395	4.33	17.104	.....	.....	....
July 18	8:35 p.m.	185	6.40	11.846	28.944	10.759	2.68
July 19	8.45 a.m.	340	3.67	12.478	.....	.....	....
July 19	11:00 a.m.	45	4.60	2.070	.....	.....	....
July 19	4:00 p.m.	50	4.51	2.255	18.224	6.777	2.69
July 19	1:30 p.m.	35	4.06	1 421	.....	.....	....

* Operated on 4 p. m. July 17; injected with 175 c.c. pancreatic perfusate directly as it came from the gland.

The marked depressor action of the perfusates may be a factor in explaining their apparent influence on glycosuria (E. G. Kirk).[9] Figure 4 shows an increase in this property if the perfusate is allowed to stand thirty hours, probably a result of autolysis caused by pancreatic digestive enzymes present in the solution. However, throughout the experiments no rise in temperature or visible signs of toxemia or depression were noted.

9. Kirk, E. G.: Arch. Int. Med. **15**:39 (Jan.) 1915.

It was suggested that the apparent negative results were due to a decomposition of the internal secretion contained in the perfusate, and that decomposition rather than concentration resulted from an hour's perfusion of the gland. The findings of Clark as to the stability of the secretion made this theory probable. Consequently, the solution

TABLE 4.—EXPERIMENTAL RESULTS FROM OBSERVATION OF DOG 30 *

Date	Time	Amount of Urine	Sugar, per Cent.	Sugar, Gm.	Total Sugar	Total Nitrogen	D/N
July 23	9:30 a.m.	90	4.87	4.183	4.183	3.384	1.26
July 24	7:30 a.m.	120	6.17	8.124	.....	.....	....
July 24	9:15 p.m.	115	4.64	5.336	13.460	9.823	1.37
July 25	9:30 a.m.	80	6.68	5.344	.....	.....	....
July 25	8:15 p.m.	40	2.61	1.044	6.388	4.392	1.45

* Pancreatectomy on Dog 30 was completed at 3:45 p. m., July 22, 1919, and the animal immediately injected with a perfusate prepared by passing defibrinated blood of a diabetic dog through the normal gland once.

TABLE 5.—EXPERIMENTAL RESULTS FROM OBSERVATION OF DOG 22 *

Date	Time	Amount of Urine	Sugar, per Cent.	Sugar, Gm.	Total Sugar	Nitrogen, Gm.	Total Nitrogen	D/N
July 11-12	7:00 a.m.	80	2.70	2.100	.....	2.296	.....	....
	8:35 a.m.	98	4.47	4.380	.....	3.900	.....	....
	7:45 p.m.	255	3.27	8.338	14.818	10.276	16.472	0.89
July 12-13	7:30 a.m.	210	3.27	6.867	.....	4.767	.....	....
	1:00 p.m.	35	3.89	1.362	.....	0.706	.....	....
	3:30 p.m.	55	2.09	1.150	.....	1.249	.....	....
	6:55 p.m.	50	1.52	0.760	10.139	1.135	7.946	1.28
July 13-14	8:30 a.m.	20	6.04	1.208	.....	0.67	.....	....
	12:30 p.m.	20	7.88	1.576	2.784	0.67	1.340	2.07

* Pancreatectomy on Dog 22 was complete at 3:30 p. m., July 10, 1919. The animal was injected immediately following pancreatectomy with 150 c.c. pancreatic perfusate as described.

TABLE 6.—DOG 2 WAS FED 480 GM. RAW, LEAN MEAT PER DAY, AND RECEIVED PLENTY OF WATER *

Date	Time	Amount of Urine	Sugar, per Cent.	Total Sugar	Total Nitrogen	D/N
April 26	10:00 a.m.	645	2.60	16.77	12.90	1.30
April 27	10:00 a.m.	427	Spilled by accident			
April 28	10:00 a.m.	350	3.00	9.11	5.950	1.54
April 29	10:00 a.m.	227	2.30	5.22	4.904	1.05
April 30	10:00 a.m.	270	3.10	8.37	5.670	1.48
May 1	10:00 a.m.	70	2.92	2.04	1.680	1.22
May 2	10:00 a.m.	240	3.20	7.68	5.280	1.45

* Complete pancreatectomy April 16.

was passed once through the gland and injected immediately into the depancreatized animal. The same technic and precautions were observed as previously described.

Figure 5 shows the typical curve from such an experiment. Glycosuria appeared six hours following pancreatectomy and rose to its maximum within thirty hours. As will be seen in Table 3, the

D/N ratios rose from 1.42 to 2.69 during the sixty hour period immediately following pancreatectomy.

A third series of experiments was then attempted in which defibrinated blood from a depancreatized animal was used instead of Tyrode's solution. It was hoped that this would be a better medium for collecting the internal secretion from the gland. Defibrinated blood from depancreatized animals had been previously shown by Drennan to have no effect on the D/N ratio in experimental diabetes.

Under light anesthesia, blood was drawn aseptically from the jugular vein of an animal depancreatized three days previously. The animal was diabetic, having a glycosuria of 3.36 per cent and a hyperglycemia of 1.22 mg. dextrose per c.c. of blood. The Munson-Walker method for blood sugar determination was used. One hundred cubic centimeters of this blood, after being defibrinated, was passed through a normal pancreas and then injected into an animal immediately following pancreatectomy.

Figure 6 shows the dextrose nitrogen curves for this experiment. There was apparently no effect on the onset of glycosuria. Table 4 shows a uniform rise of the D/N from 1.26 to 1.45 during a period of seventy-five hours following injection.

CONCLUSIONS

1. As compared with the figures reported in the literature, especially by Lusk, the D/N ratios are uniformly low.

2. The percentage of sugar in the urine and the total sugar excretion per day show wide variations both on a constant diet and during starvation.

3. Although the total nitrogen excretion in some animals was relatively constant, others under identical conditions showed marked variations.

4. All factors within our control, such as diet, water, etc., did not maintain a D/N ratio sufficiently constant to be of use in carrying out the first series of experiments.

5. Perfusates prepared by passing glucose-free Tyrode's solution for one hour through the blood vessels of a normal pancreas did not delay the onset of diabetes.

6. Two exceptions to the above conclusion are recorded. It seems unlikely, in view of the work of A. J. Carlson and co-workers on the Control of Diabetes in Pregnancy, that the fetuses described in these animals could have altered the course of diabetes. Since we were unable subsequently to confirm these results, they are merely of suggestive value.

7. Maximum elevation of glycosuria is delayed by injection of pancreatic perfusates.

8. The influence on glycosuria is probably apparent and not real, since it is followed by a compensatory rise. This effect may be explained by the action of depressor substances shown to be present in the perfusates.

9. Solutions passed once through the gland when injected intravenously showed no effect either on the onset or course of experimental diabetes.

10. Defibrinated blood drawn from pancreatectomized animals and passed once through the normal pancreas had no effect on experimental diabetes.

11. The internal secretion of the pancreas, if it can be obtained by the perfusion experiments described, may be too labile or in too low concentration to influence the sugar metabolism of the diabetic animal.

We wish to record our thanks to Dr. F. C. Koch for his many valuable suggestions and his untiring interest in our work.

BOOK REVIEWS

THE EVOLUTION OF MODERN MEDICINE. A Series of Lectures Delivered at Yale University on the Silliman Foundation in April, 1912, by Sir William Osler, Bt., M.D., F.R.S.

Nearly ready for publication, the proofs partially corrected by Sir William, the great war interrupted the final correction and completion of this volume. The work was completed by Fielding H. Garrison, Harvey Cushing, Edward P. Streeter, and Leonard L. Mackall, who have carried out the author's plans and wishes in every respect. The volume represents Osler at his best—not only as a physician but as a scholar, a man of letters and an historian—while the publishers have achieved a setting worthy of the content. Composed originally for a lay audience and popular consumption, it will furnish inspiration to physicians as well, tracing as it does the devious course of medical progress and struggle to the present, and one needs no medical knowledge to follow the golden thread. In the introduction he considers Egyptian, Assyrian, Babylonian and Oriental medicine, with evidence of early operative and therapeutic procedures and directions. Then Greek medicine with the contributions of both mythology and the philosophers—medieval medicine with the isolated centers in universities throughout Europe—the renaissance and development of anatomy and physiology —modern medicine, and the rise of preventive medicine. Osler himself called it "an aeroplane flight over the progress of medicine through the ages." But, in spite of the necessary brevity, one gets an amazingly clear picture of the individuals and the events, due partly to the numerous cuts and engravings, themselves, the author's choice from an enormous bulk of extant material.

The volume is a delightful addition to the physician's library. With it he can journey for a time away from his twentieth century setting to bygone times and other places, returning with a happier perspective and a clearer understanding of his own position in the evolution of medicine.

HUMAN PARASITOLOGY. By Damaso Rivas. Philadelphia and London: W. B. Saunders Co., 1920.

This book is written primarily as a textbook of the animal forms parasitic in man, and while a large part is devoted to the classification and description of these parasites, the author has added brief chapters on certain phases of bacteriology, serology and laboratory diagnosis. These are not especially attractive, as they, in themselves, are sufficiently comprehensive to be considered in separate texts rather than as addenda to a textbook of the animal parasites of man.

The first chapters of the book deal with the historical features of animal parasitology, the relation of parasite to host and the effect of animal parasitism on a host. Descriptions of the parasitic forms are complete. The classification is strictly zoologic, and somewhat confusing, at least for the average physician. However, it is readily understood by those with a broad zoologic training, and the book, therefore, will appeal more to such physicians. The literature references of a book now being offered to physicians as a text of the animal parasites of man should include recent work in parasitology, especially as such a book is intended for more than a laboratory guide.

PRECIS DE PARASITOLOGIE, par le Pr Guiart, professeur à la Faculté de médecine de Lyon et à la Faculté de médecine de Cluj. Ed. 2, 1922, 575 pages, with 462 illustrations. (*Bibliothèque du Doctorat en Médecine*, Gilbert et Fournier) (*Librairie J.-B. Baillière et fils, 19, rue Hautefeuille, Paris*).

This volume is one of the thirty-five composing the "Bibliothèque du Doctorate en Médecine" collected under the supervision of Gilbert and Fournier.

In undertaking the work the editors state their reasons frankly. The sum of the knowledge required today of the student and practitioner of medicine is large, and increasing daily, and in the relatively short time devoted to the acquisition of the knowledge necessary, there is a large amount of information which can neither be covered in the classes nor remembered afterward, especially the minutiae and less essential details of the subdivisions or specialties of medicine. In undertaking to present the series, the editors have endeavored to obtain the outstanding authorities in each division. The present second edition is the volume on parasitology, the result of twenty-four years' specialization by the author, Professor Guiart. It is written for the student and physician, contains only material useful to them, and retains the medical point of view in the study of the parasites, followed by concise descriptions of the diseases produced by them. The volume is profusely and clearly illustrated, well indexed, and in every respect attains the editors' desire to present all that is indispensable in the knowledge of parasitology in a clear, concise volume.

ZUR THERAPIE DES KARZINOMS MITT RONTGENSTRAHLEN. Vorlesungen Ueber Die Physikalischen Grundlagen Der Tiefentherapie. Von Prof. Dr. Fr. Dessauer, Direktor Des Instituts Für Physikalische Grundlagen Der Medizin An Der Universität Frankfurt A. M. 30 Illustrations. Dresden and Leipzig: Theodor Steinkopff, 1922.

In the form of four lectures the author outlines the roentgen-ray therapy of deep lying cancer by the use of the Roentgen rays of extremely short wave length combined with copper filters, large areas and increased distance, so as to obtain a high dose quotient at the depth of the disease. Only by this means is an adequate dosage of rays administered to the cancer cells without injuring the overlying tissues. The depth of ten cm. is used as a standard for computing ray absorption, and in order to generate a beam rich in the rays of high penetrating character a larger capacity tube must be used combined with an electrical transformer delivering a current of much higher potential than has been the practice in the past. Two hundred thousand volts excites the tube, and the beam is filtered through a copper filter of a thickness the major fraction of a millimeter. This absorbs much of the heterogeneous discharge and allows the passage of short wave lengths only. To obtain a sufficient dose the time must be prolonged. Scattered radiation within the tissues is taken advantage of by increasing the area of tissue treated. It is found that multiple small portals of entry and many angles of cross-fire are not necessary. Much attention must be paid to the percentage of rays absorbed at various levels, however, so that when cross fire dosage is given the proper summation of effects is obtained throughout the pathologic mass. In malignancies located in the middle of the body a heavy exposure is made from the front, back and sides to build up in the center a combined dosage sufficient to destroy carcinoma. The ratio of skin to depth dose, or dose quotient, is further increased by increasing the tube-skin distance. The physics underlying these technical considerations is explained and illustrated by many cuts, tables and graphs. Abstracts of numerous other articles relating to deep therapy are appended.

THE LETHAL WAR GASES: PHYSIOLOGY AND EXPERIMENTAL TREATMENT. Frank P. Underhill, Ph.D., New Haven, Yale University Press, 1920.

This octavo volume of 310 pages embodies a report of work conducted during the late war under the author's direction by the section on Intermediary Metabolism of the Medical Division of the Chemical Warfare Service, organized originally by the Bureau of Mines. The work of this section consisted largely in exposing dogs during single or repeated periods of different time lengths to chlorin, phosgene or chlorpicrin in known and varying concentrations. Thorough and systematic examinations were made of the gassed animals under exactly specified conditions as to the clinical symptoms and their course, of the mor-

phologic and volume changes in the tissues and blood, the chemical changes in the blood and urine, the respiratory function, the acid base balance, etc. The findings are tabulated in detail together with the writer's analysis and interpretation. Having established a standard for control, experiments were performed with different therapeutic procedures.

One gathers from the data that the most notable gross changes observed consisted of edemas, especially of the lungs, with a fall in the volume of the blood, a rise in the blood concentration, and a failing circulation, this accounting, according to Underhill, for those observed changes of the respiratory function referable to oxygen starvation of the tissues with a fall of temperature and finally suspension of vital activities. The immediate cause of death must, he believes, be assigned to blood concentration. Acidosis, as measured by the methods selected, was missed except in the later stages of the picture. The therapeutic measures that yielded the most favorable results were those directed toward increasing the blood volume and dilution, namely, bleeding properly carried out and followed by a restoration of water, with alkali administration when acidosis was demonstrable. The work is notable for its thoroughness and accuracy. Apart from the value that it would have in the case of future warfare with gases it represents a piece of inductive research of exceptionally high order, and contains a mass of data and the description of methods that may well find their application in the study of toxicology in general.

THE MECHANICS OF THE DIGESTIVE TRACT. By WALTER C. ALVAREZ, M.D., Assistant Professor of Research Medicine University of California Medical School. Pp. 200. 22 Illustrations. Paul B. Hoeber, New York City.

This monograph is written to defend or establish the following theses from experimental and clinical data: (1) The normal and pathologic activities of the intestine are due to a polarized gradient in the intestinal musculature. There are no local reflex actions in the intestine itself. Auerbach's ganglionic plexus functions only in connection with the extrinsic nerves. All the local variations in action shown in different regions of the intestine are due to change in the rhythmicity of the muscular gradient. (2) That many, if not all, of the symptoms usually referred to a disordered intestine are caused by reversal of the gastro-intestinal peristalsis.

The first seven chapters deal with the facts and speculations on which the theory of muscular gradient of intestine action is based. Chapter IX deals with the practical application of this theory to conditions of gastro-intestinal disease in man. Chapter X deals with the supposed symptoms of reversed peristalsis. Chapter XI contains a critique of the current notions of "vagotonia" and "sympatheticotonia." The last chapter deals briefly with experimental methods, and the volume ends with a good bibliography of 450 titles.

The author is both a clinician and a laboratory worker. He has enthusiasm, and a good knowledge of the literature. The book is, therefore, a valuable compilation and treatise on the intestine, and is of interest to all medical men and physiologists. While, in general, the author is scientific in the analysis of facts and theories, in a few cases he becomes a special pleader and misconstrues facts in favor of his two main theses. He speaks of pieces of the stomach and intestine as "strips of muscle," when, as a matter of fact, they are strips of muscle, ganglia and nerves. On page 4 he says: "Most of us think of the pupillary response to light as a complicated cerebral reflex." That view may be held by the ignorant; the others know that in the mammal it is a midbrain, not a cerebral reflex.

On page 14 he says: "Another function of the Auerbach's plexus is probably to make the intestinal muscles respond properly to stimuli coming from the underlying mucous membrane. These stimuli are taken up by Meissner's plexus and transmitted to Auerbach's by connecting fibres." This is in all essentials a reflex act, and yet the author devotes a large part of the book to disprove reflex action in the intestine itself.

Alvarez's recurring objection to local reflexes and the nervous action in the motor activities of the intestine is that "nervous action is not really understood." Granted! But is muscle contraction, or cell growth, or, in fact, any fundamental physiologic phenomenon really understood today? We do not understand the mechanism of memory, but must we, therefore, exclude memory as a factor in animal behavior? Nobody denies today that visceral as well as skeletal muscles, placed in certain artificial solutions in vitro, may be made to contract rhythmically. But these activities of dying tissues in artificial mediums have probably no relation to the normal activities of these tissues in the intact animal. Theories built on such nonphysiologic experimentation may help to explain, e. g., paralysis agitans or St. Vitus dance, but not normal neuromuscular coordination.

The following symptoms, according to the author, are due to reverse peristalsis in the intestine: vomiting, regurgitation, heart burn, belching, nausea, biliousness, coated tongue, foul breath, feeling of fulness soon after beginning a meal, globus, hiccough. The interested reader must judge for himself how successful the author is in these explanations. How is nausea and vomiting started by the smell or sight of disgusting objects to be explained by reverse peristalsis in the gut without admitting that the reversal of the peristalsis is itself a nervous action? In the paragraph on "Globus," the author offers this bit of physiologic speculation: "A few times in my life I have happened to swallow while a wave of regurgitation was on its way up the esophagus, and when the two waves met there was a painful tearing feeling. It may be that globus is brought about in that way." Alvarez meets the objection that reverse peristalsis is rarely seen even in marked gastro-intestinal motor disturbance by the assumption that such peristalsis, too feeble to move the intestinal content toward the stomach, or to be detected by the Roentgen ray, still produces nausea and allied mental states. He fails to make clear why reversal of peristalsis should cause central symptoms, while normal peristalsis does not, or why the reversed peristalsis which is normal (colon; duodenum) fails to cause untoward effects. The medical practitioner will probably be most interested in the "practical application" in Chapter IX. At the end of this chapter we read: "Some one may ask: In what way does the idea of a gradient altered by disease influence our method of treatment? The answer is that so far little has been done because therapeutists have not been thinking along these lines." The author hopes for drugs to restore the normal gradient, but at present can suggest only a smooth diet, a remedy that helps or fails, irrespective of the theories of intestine mechanism.

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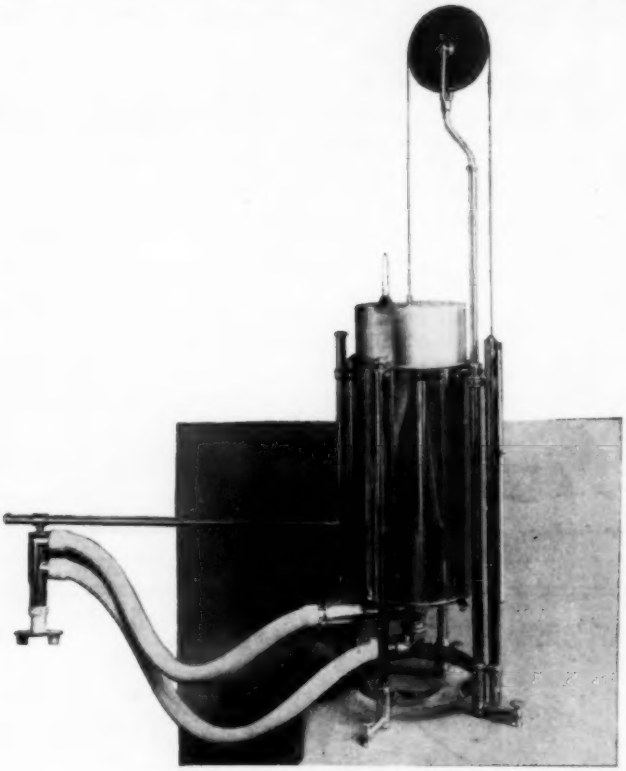

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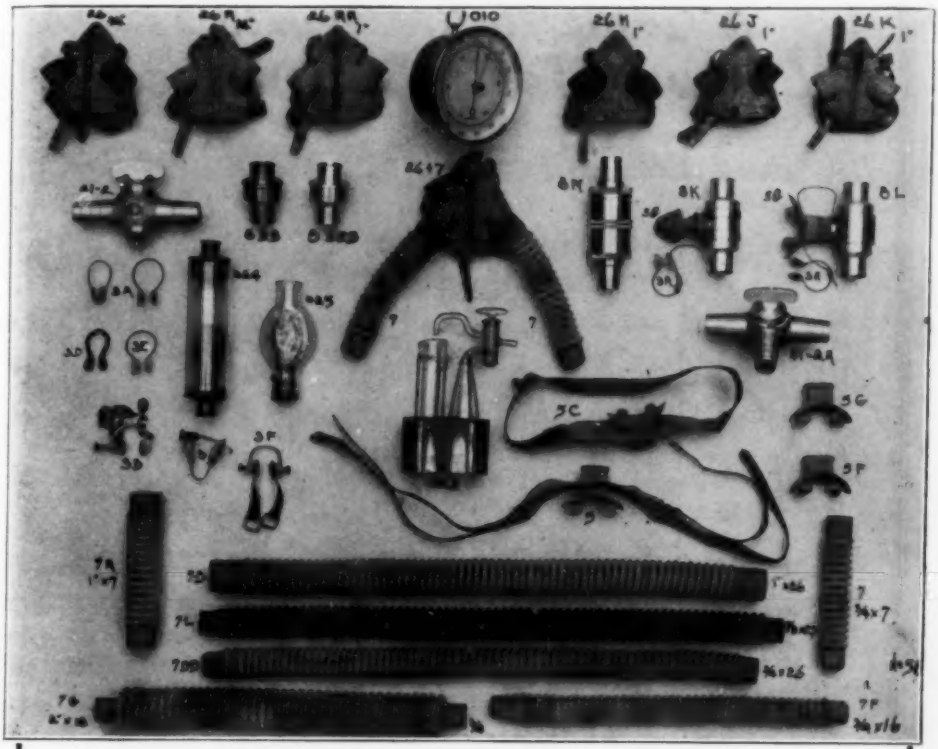

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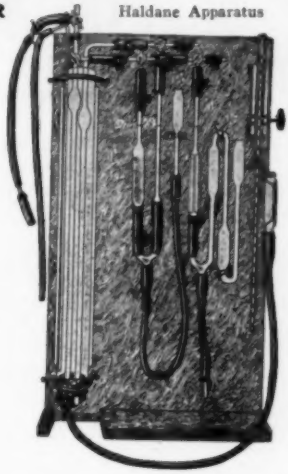

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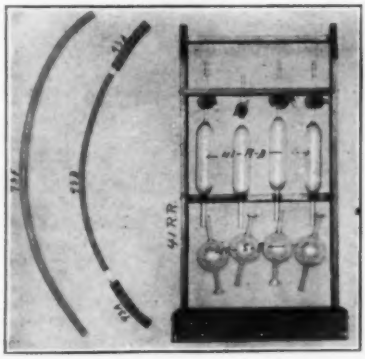

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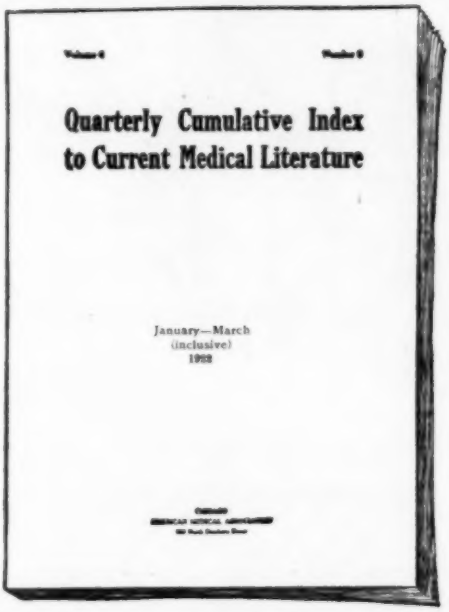

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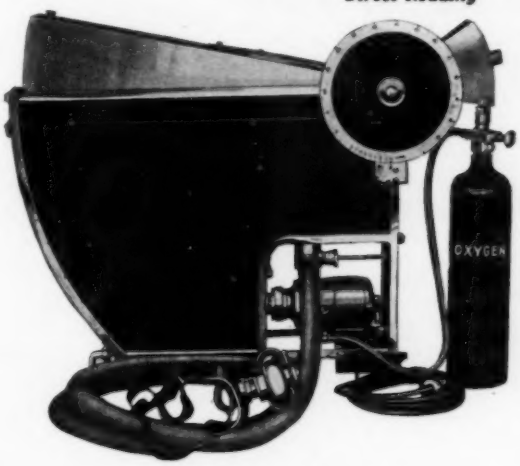

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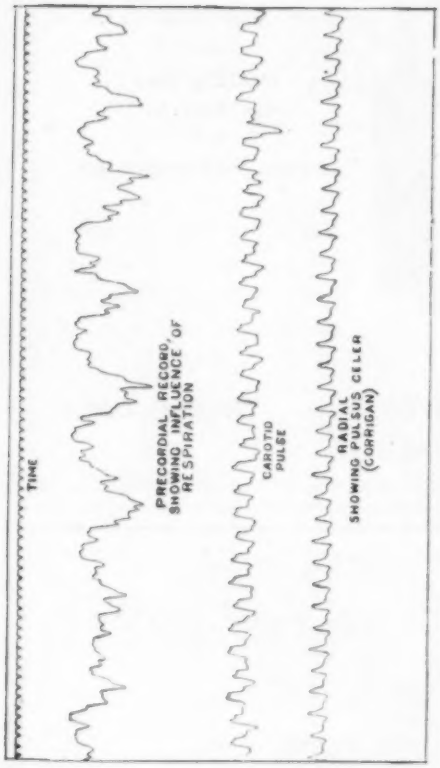

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